



Reproxalap Activity and Estimation of Clinically Relevant Thresholds for Ocular Itching and Redness in a Randomized Allergic Conjunctivitis Field Trial

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ABSTRACT

Introduction: This clinical trial assessed the activity of reproxalap, a novel reactive aldehyde species modulator, and estimated clinically relevant thresholds for changes in ocular itching and redness in an allergic conjunctivitis field trial.

Methods: This was a randomized, double-masked, vehicle-controlled phase 2 trial. Patients with ragweed-associated allergic conjunctivitis were assessed over 28 days in an environmental setting with approximately four doses per day of either 0.25% reproxalap, 0.5% reproxalap, or vehicle. Patients recorded ocular itching, redness, tearing, and eyelid swelling scores (each with a 0–4 scale, except for a 0–3 scale for swelling), and completed the Allergic Conjunctivitis Quality of Life Questionnaire at the beginning and end of the trial.

Results: Mixed model of repeated measures analysis demonstrated statistically lower itching and tearing scores (pooled $P = 0.026$ and $P < 0.001$, respectively) and numerically lower redness and eyelid swelling scores than vehicle on days when pollen exceeded the 95th percentile value. Using three anchor-based and three distribution-based approaches, the meaningful within-patient change and the between-group meaningful difference for patient-reported ocular itching and redness was estimated to be approximately 0.5. The most common treatment-emergent adverse event associated with reproxalap was transient irritation upon instillation.

Conclusion: In a field clinical trial, reproxalap was well tolerated and superior to vehicle in reducing ocular itching on high-pollen days. The clinical meaningfulness threshold estimates of 0.5 units are among the first such calculations generated for the standard ocular itching and redness scores, providing important context for the clinical interpretation of clinical trials in allergic conjunctivitis.

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PLAIN LANGUAGE SUMMARY

While allergic conjunctivitis affects millions of patients worldwide, treatments with new mechanisms have not been introduced in decades. Reproxalap, a medicine being investigated as a treatment for allergic conjunctivitis, works by regulating reactive aldehyde species—molecules that are increased in a variety of inflammatory diseases. This clinical trial assessed the activity of reproxalap and estimated what amount of change in ocular itching and redness should be considered clinically important. Patients with ragweed-associated allergic conjunctivitis were assessed over 28 days and were given one of three possible eye drops at approximately four doses per day: 0.25% reproxalap; 0.5% reproxalap; or vehicle, which was composed of the same ingredients but does not contain reproxalap. Patients recorded ocular itching, redness, tearing, and eyelid swelling (all scales ranged from 0 [none] to 4 [severe] except for eyelid swelling, which ranged from 0 to 3), and completed a quality-of-life questionnaire on allergic conjunctivitis at the beginning and end of the trial. The results indicated that reproxalap was significantly better than vehicle in reducing itching and tearing scores and was better than vehicle in reducing redness and eyelid swelling scores on days when pollen counts were high. The trial also suggested that a reduction in ocular itching and redness scores of approximately 0.5 or more (scale 0–4) is likely to be clinically important. Overall, reproxalap was well tolerated and no safety concerns were noted. The most common side effect was transient ocular discomfort after eye drop administration.

Keywords: Allergic conjunctivitis; Clinical relevance; Clinical trial; Ocular itching; Ocular redness; RASP modulator; Reproxalap

Key Summary Points

Why carry out this clinical trial?

This clinical trial was carried out to assess the activity of reproxalap and estimate clinically relevant thresholds for changes in ocular itching and redness in an allergic conjunctivitis field trial.

What did the clinical trial ask/what was the hypothesis of the clinical trial?

It was hypothesized that reproxalap would be superior to vehicle in reducing the signs and symptoms of allergic conjunctivitis. Additionally, what are the relevant thresholds for patient-reported ocular itching and redness scores?

What was learned from the clinical trial?

The clinical meaningfulness threshold estimates of 0.5 units were derived for the standard patient-reported ocular itching and redness scores.

What were the clinical trial outcomes/conclusions?

Reproxalap was well tolerated and superior to vehicle in reducing ocular itching on high-pollen days. The clinically relevant threshold for changes in ocular itching and redness scores (range 0–4) is approximately 0.5 units.

INTRODUCTION

Allergic conjunctivitis affects millions of patients worldwide, but novel therapeutic mechanisms have not been introduced in decades. Although topical antihistamines are widely used for the treatment of allergic conjunctivitis, up to 60% of patients require

additional medication, including topical corticosteroids, which can lead to ocular toxicity [1, 2]. Therefore, new drugs for ocular allergy with alternative mechanisms of action that can be combined with existing therapies are desirable [3]. One such mechanism that represents a novel approach for the treatment of ocular inflammation is the modulation of reactive aldehyde species (RASP), which are small molecule, systems-based mediators of cytokine release [4, 5]. Reproxalap, a topical ocular RASP modulator, has demonstrated activity in phase 2/3 trials in noninfectious anterior uveitis, dry eye disease, and allergic conjunctivitis [6–10].

In both controlled and environmental settings, the typical method for assessment of activity in patients with allergic conjunctivitis includes measurement of ocular itching and redness on a 0 (none) to 4 (severe) scale [9–11]. Although the clinically important difference in ocular itching score between treatment groups has traditionally been set at 1 unit [12], evidence justifying 1 unit as a meaningful difference is lacking. Distribution-based techniques (e.g., effect sizes, standard deviation and, standard error of measurement) are typically used to estimate clinically meaningful between-group magnitudes, whereas anchor-based techniques, which compare changes in scores with an external indicator (anchor) as a reference, are typically used to estimate meaningful within-patient changes [13–15]. Remarkably, to our knowledge, clinically relevant thresholds derived from either distribution-based or anchor-based approaches for patient-reported ocular itching and redness scores have not been published.

A randomized, double-masked, parallel-group phase 2 trial in ragweed-sensitive patients with allergic conjunctivitis was performed over 28 days to assess the activity of two concentrations of reproxalap compared with vehicle in an environmental setting. In addition, the signs, symptoms, and quality-of-life (QOL) data from the trial were incorporated across three distribution-based and three anchor-based approaches to estimate clinically meaningful between-group and within-patient differences in patient-reported ocular itching and redness scores.

METHODS

Trial Design

Patients with seasonal allergic conjunctivitis were enrolled in a multicenter, randomized, double-masked, vehicle-controlled, parallel-group phase 2 trial designed to evaluate the activity of two concentrations of topical ocular reproxalap (0.25% and 0.5%) relative to vehicle in an environmental setting over 28 days during ragweed pollen season. The trial consisted of five visits: two screening visits during which skin test and conjunctival challenge sensitivity to ragweed was confirmed, a visit to confirm continued eligibility after 6 days of four-times-daily plus as-needed dosing of an artificial tear, a visit 2 weeks after test article (reproxalap or vehicle) administration was initiated, and a visit 2 weeks later at the end of the trial. Patients were randomly assigned 1:1:1 according to a predetermined randomization sequence to receive either 0.25% reproxalap, 0.5% reproxalap, or vehicle four times daily and up to four more times per day as needed. All test articles were preservative-free and did not contain benzalkonium chloride. An unmasked and independent biostatistics vendor generated a randomization list for clinical sites to assign masked clinical trial drug to patients. Patients, investigators, and the sponsor were masked to treatment assignment throughout the trial.

The trial (ClinicalTrials.gov, NCT03660878) was performed in the USA in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, the International Council for Harmonisation Guideline on Good Clinical Practice, and all applicable local regulatory requirements and laws. The trial was carried out with approval from an institutional review board (Alpha IRB, San Clemente, CA, USA), informed consent was obtained from the patients, and the research followed Health Insurance Portability and Accountability Act regulations.

Patient Selection

Adult patients aged 18 years or more were eligible to participate in the trial if they met the following criteria: history of allergic conjunctivitis, positive skin test to ragweed pollen (i.e., greater wheal size than the negative control or same wheal size as negative control with presence of itching), baseline investigator-assessed conjunctival redness and at least one patient-reported symptom (ocular itching, tearing, or eyelid swelling) scores of at least 1 (all scales ranged from 0 [none] to 4 [severe] except for eyelid swelling, which ranged from 0 to 3), and conjunctival ragweed challenge-induced ocular itching and redness scores of at least 2 for both eyes. Patients were excluded for any clinically significant slit-lamp findings or a history of inflammatory conditions, infectious diseases, or ocular surgeries that may have interfered with the conduct of the trial. Other exclusions included use of antihistamines within 3 days prior to screening, corticosteroids within 14 days prior to screening, or immunotherapeutic agents within 60 days prior to screening.

Clinical Trial Assessments and Endpoints

Patient-reported ocular itching, ocular redness, ocular tearing, and eyelid swelling scores were recorded three times daily for 28 days. All scores, which were averaged by day, were derived from Ora Calibra® scale (Ora, Inc., Andover, MA, USA) scores ranging from 0 (none) to 4 (severe) except eyelid swelling, which ranged from 0 (none) to 3 (severe). Half-unit increments were possible for the ocular itching scale. The Allergic Conjunctivitis Quality of Life Questionnaire (ACQLQ®; Ora, Inc.), a 17-item assessment scale (each item rated on a 0 [not bothered] to 6 [extremely bothered]) was performed on the first and last days of test article administration concurrent with assessment of symptom scores [16, 17]. The itching and redness ACQLQ items were used to assess the QOL impact relative to itching and redness scores. Safety assessments included visual acuity, slit-lamp biomicroscopy, undilated

fundoscopy, intraocular pressure, and adverse events (AEs).

Statistical Analysis

The trial was exploratory and not formally powered. Given that reproxalap had not been previously tested in an allergen chamber, no primary or secondary endpoints were designated. Mixed-effect models for repeated measures (MMRM) were used to assess change from baseline (the first day of treatment) of symptom scores over all time points in aggregate, with treatment group and day as factors. Subset MMRM analyses were performed on high-pollen days, defined as days when pollen counts met or exceeded the 95th percentile for weed pollens (i.e., 325 grains per cubic meter) for individual and pooled reproxalap groups, according to the American Academy of Allergy, Asthma, and Immunology's National Allergy Bureau [18]. Rank-based nonparametric testing for longitudinal data was used as a sensitivity analysis for the pooled-group MMRM subset results [19]. Ocular itching and redness symptom scores were regressed versus the respective ACQLQ items with the γ intercept set at 0. Safety assessments were evaluated with summary statistics.

Three anchor-based techniques (comparison of the ACQLQ as a QOL anchor to itching and redness scores) were performed to assess the meaningful within-patient change in patient-reported ocular itching and redness scores: slope of the relationship between scores and the respective ACQLQ item, upper limit of the 95th percentile confidence interval of the change in scores for patients with no change in the respective ACQLQ item [15, 20], and the subtraction method (i.e., change in scores for patients with 1-point improvement in the respective ACQLQ item minus change in scores for patients with no improvement in the respective ACQLQ item) [21]. Three distribution-based techniques were performed on the itching and redness scores to estimate a relevant between-group difference: 10% of the range of the scoring scales (0–4) [22], half of the baseline standard deviation [23], and standard error of

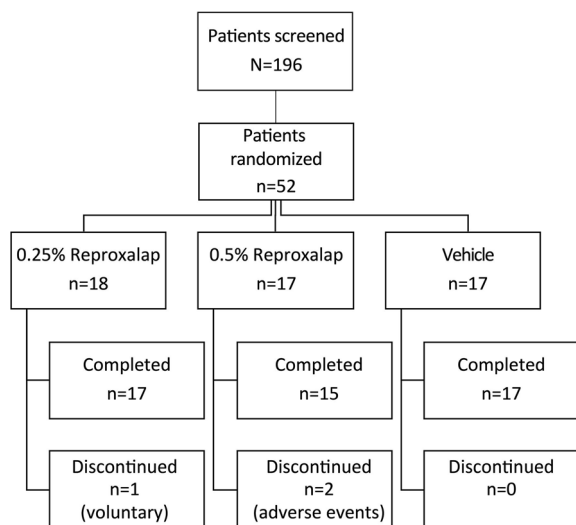


Fig. 1 Patient disposition

the mean using Cronbach's alpha across all symptom scores in aggregate as the test reliability [24, 25].

RESULTS

Patient Disposition, Baseline Characteristics, Dosing, and Pollen Exposure

Patient disposition is diagrammed in Fig. 1. A total of 196 patients with allergic conjunctivitis were screened, and 52 were randomized and treated between September 9, 2018 and December 20, 2019 at three clinical sites in the USA. Most screen failures were due to insufficient ocular itching and redness either at baseline or after conjunctival challenge. There were three discontinuations among the randomized patients: one in the 0.25% reproxalap group discontinued for voluntary reasons not otherwise specified and two in the 0.5% reproxalap group were withdrawn because of AEs (ocular irritation in one patient considered related to drug and development of brain lesions in one patient deemed unrelated to drug).

Baseline demographic characteristics were generally comparable across groups (Table 1). Compliance with drug administration was high; the average eye drops per day for all patients in

the 0.25% reproxalap, 0.5% reproxalap, and vehicle groups were 3.9, 3.6, and 3.9 drops, respectively. As-needed dosing was minimal; two, four, and three patients required more than four eye drops during any single day in the 0.25% reproxalap, 0.5% reproxalap, and vehicle groups, respectively. Pollen exposure was significantly lower than expected, and the most common daily pollen count was 0 grains per cubic meter (Fig. 2). Five patients in each reproxalap group and four patients in the vehicle group were exposed to American Academy of Allergy Asthma, and Immunology's National Allergy Bureau weed pollen levels at the 95th or higher percentile (325 grains per cubic meter) for an average of 7 days, and were therefore designated high-pollen patients [18].

Efficacy

No statistically significant changes were observed across treatment groups for any patient-reported ocular symptom. For high-pollen patients, however, all patient-reported symptoms diminished over the course of the trial in patients treated with reproxalap (Fig. 3). Improvement (i.e., decreases) from baseline in ocular tearing was statistically superior to that of vehicle for each reproxalap group ($P = 0.005$ and $P < 0.001$ for 0.25% reproxalap and 0.5% reproxalap, respectively) and for pooled reproxalap groups ($P < 0.001$) (Fig. 3a). Improvement in ocular itching over that of vehicle was numerically superior for both reproxalap groups ($P = 0.058$ for each) and achieved statistical significance when reproxalap groups were pooled ($P = 0.026$) (Fig. 3b). Improvement in ocular redness (Fig. 3c) and eyelid swelling (Fig. 3d) was not statistically significant for either reproxalap group in comparison to vehicle, although improvement in ocular redness approached statistical significance for 0.25% reproxalap ($P = 0.071$). Non-parametric statistics were consistent with the MMRM findings for the high-pollen patients.

Table 1 Baseline demographic characteristics

	0.25% Reproxalap, N = 18	0.5% Reproxalap, N = 17	Vehicle, N = 17	All patients, N = 52
Age (years)				
Mean (SD)	49.0 (14.6)	42.8 (16.6)	43.8 (11.6)	45.3 (14.4)
Median	53.5	43.0	38.0	45.5
Range	25–71	19–78	23–66	19–78
Age category (years), <i>n</i> (%)				
< 65	16 (88.9)	16 (94.1)	16 (94.1)	48 (92.3)
≥ 65	2 (11.1)	1 (5.9)	1 (5.9)	4 (7.7)
Sex, <i>n</i> (%)				
Male	5 (27.8)	6 (35.3)	6 (35.3)	17 (32.7)
Female	13 (72.2)	11 (64.7)	11 (64.7)	35 (67.3)
Ethnicity, <i>n</i> (%)				
Hispanic or Latino	10 (55.6)	9 (52.9)	11 (64.7)	30 (57.7)
Not Hispanic or Latino	8 (44.4)	8 (47.1)	6 (35.3)	22 (42.3)
Race, <i>n</i> (%)				
Asian	1 (5.6)	0	0	1 (1.9)
Black or African American	1 (5.6)	0	1 (5.9)	2 (3.8)
White	15 (83.3)	17 (100.0)	16 (94.1)	48 (92.3)
Other	1 (5.6)	0	0	1 (1.9)
Iris color, <i>n</i> (%)				
Black	1 (5.6)	0	1 (5.9)	2 (3.8)
Blue	3 (16.7)	3 (17.6)	2 (11.8)	8 (15.4)
Brown	10 (55.6)	10 (58.8)	13 (76.5)	33 (63.5)
Hazel	1 (5.6)	2 (11.8)	1 (5.9)	4 (7.7)
Green	3 (16.7)	2 (11.8)	0	5 (9.6)

Estimation of Ocular Itching and Ocular Redness Clinical Relevance Thresholds

A high degree of correlation between patient-reported ocular itching ($r = 0.87$) and redness ($r = 0.88$) scores and the corresponding itching and redness items of the ACQLQ was demonstrated ($P < 0.001$ for each) (Fig. 4). The regression slopes for itching and redness were 0.46

and 0.59, respectively, indicating symptom score change per unit change on the appropriate ACQLQ item. During the 28 days of the trial, mean itching and redness score changes (upper 95th percentile confidence interval) for patients with no change on the appropriate ACQLQ item were 0.03 (0.41) and 0.39 (0.66), respectively. Similarly, mean itching and redness score changes for patients with a 1-unit

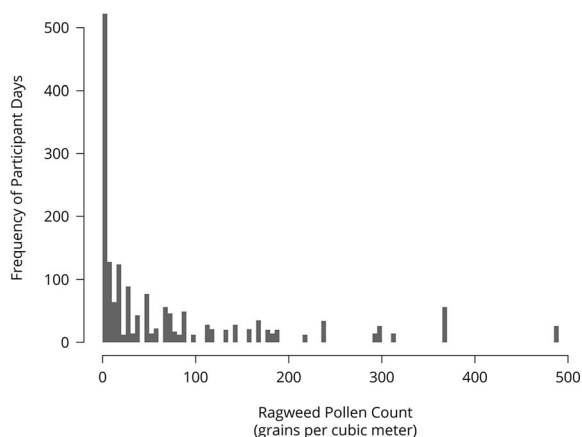


Fig. 2 Ragweed pollen count by patient day. Frequency represents days across all patients by pollen count

improvement on the respective ACQLQ item were 0.81 and 0.80, respectively, resulting in subtraction method differences of 0.78 for itching and 0.41 for redness (Fig. 5a). Distribution-based approaches yielded results similar to those of the anchor-based methods. Ten percent of the scale range (0–4) is 0.4 for the symptom scores. The standard errors of the means for itching and redness scores were 0.38 and 0.41, respectively. Half of the baseline standard deviation was 0.43 for itching and 0.46 for redness scores (Fig. 5b).

Safety and Tolerability

Both concentrations of reproxalap were well tolerated. Treatment-emergent AEs (TEAEs) related to test article were observed in 13 patients (25%) following exposure to 0.25% reproxalap, 16 patients (31%) following exposure to 0.5% reproxalap, and one patient (2%) following exposure to vehicle. Approximately 42% of patients experienced no TEAEs, and no patients experienced a serious AE related to therapy. Overall, the most common TEAEs were transient irritation upon instillation of the drug. Changes from baseline in best-corrected visual acuity, slit-lamp biomicroscopy, dilated funduscopy, and intraocular pressure assessments did not reveal any clinically significant findings, as assessed by the site investigators.

DISCUSSION

The results of the present trial highlight the challenge of controlling pollen exposure during field-based assessments of allergic conjunctivitis. Figure 2 illustrates the striking numerical skew toward a pollen count of 0 (grains per cubic meter) during the trial, indicating that most patients were not exposed to target levels of pollen (at least 95th percentile). Compounding the problem of variability in allergen exposure, many patients monitor pollen counts to avoid exposure during high-pollen days. The variability of pollen exposure in field trials suggests that conjunctival challenge trials and real-world allergen chamber exposures may be more efficient designs for the assessment of drug activity in allergic conjunctivitis [9, 10]. Nonetheless, consistent with prior clinical results, the activity of reproxalap over vehicle across all four symptom scores, which were statistically significant for pooled itching ($P = 0.026$) and tearing ($P < 0.001$) scores, during high-pollen days (Fig. 3) suggests activity of reproxalap in ameliorating allergic conjunctivitis symptoms [9, 10]. Because the exposure to high-pollen days in the clinical trial was limited, both parametric and nonparametric statistics were employed, yielding similar outcomes. Larger field trials of reproxalap are needed to confirm the results.

Notwithstanding the longtime use of patient-reported symptom scores in allergic conjunctivitis trials, the determination of clinically important thresholds for such scores has not been previously described [11]. In the present trial, the ACQLQ was used as an allergic conjunctivitis-specific QOL assessment to anchor the utility of itching and redness symptom scores [16, 17]. A statistically significant correlation was observed between ACQLQ itching and redness items and the symptom scores (0.88 and 0.87, respectively; each $P < 0.0001$), and the slopes of the correlations were 0.46 and 0.59, respectively (Fig. 4). The slopes imply that for each measurable change in QOL, itching and redness scores changed by approximately 0.5 units, an estimate of the meaningful within-patient change. Two other

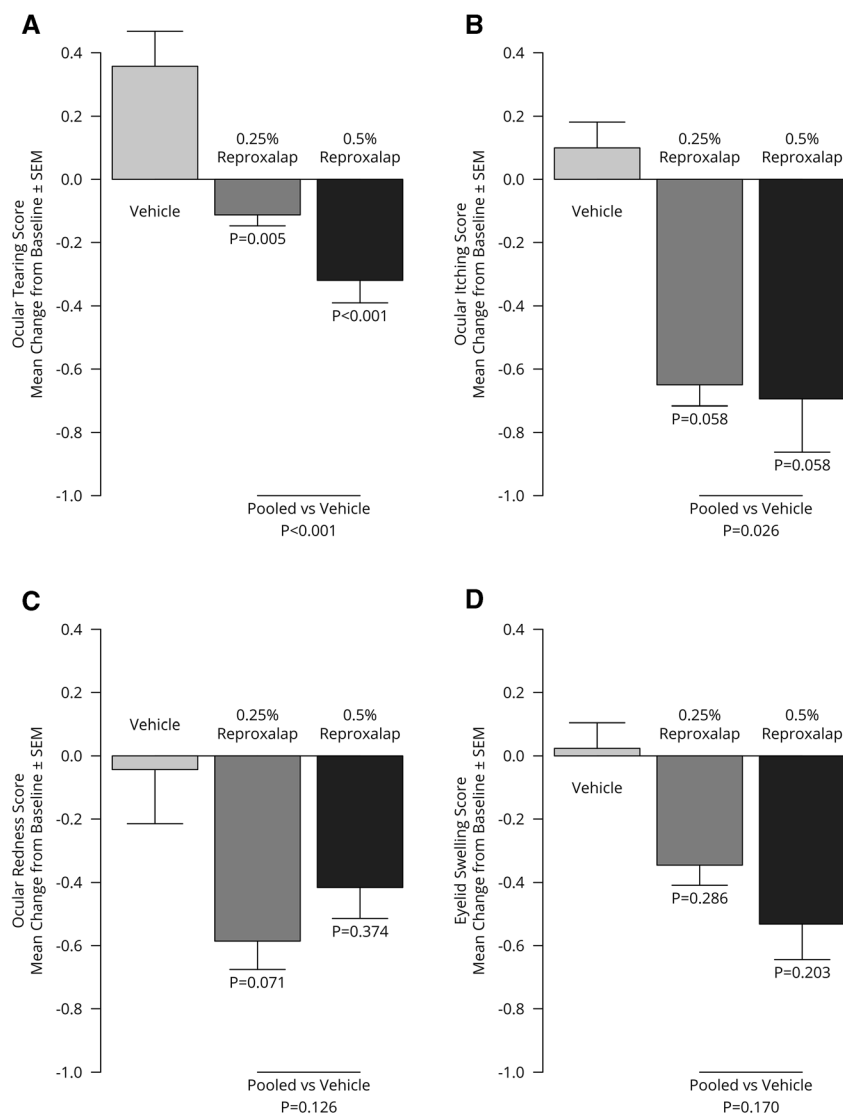


Fig. 3 Patient-reported symptom scores for **a** ocular tearing, **b** ocular itching, **c** ocular redness, and **d** eyelid swelling during high-pollen days. The range of each scale is 0 (none) to 4 (severe) except for eyelid swelling, which is 0–3. *P* values were derived from mixed-effect models for repeated measures analysis of change from baseline (the

first day of treatment) over all time points in aggregate through the end of the trial (day 28). High pollen was defined as > 95th percentile weed pollen count (325 g/m^3) [16]. SEM, standard error of the mean

anchor-based assessments, the subtraction method and the 95th percentile confidence interval upper limit for patients with no change in ACQLQ scores, were consistent with the regression results for both itching and redness scores (Fig. 5b) [20, 21]. Distribution-based assessments used to estimate between-group meaningful differences also yielded a 0.5-unit

threshold (Fig. 5a). Thus, for the 0–4 ocular itching and redness patient-reported scales, thresholds for clinically meaningful within-patient change, which could be used for responder analyses, and between-group difference, which could be used to compare treatment groups, were deemed to be approximately 0.5 units.

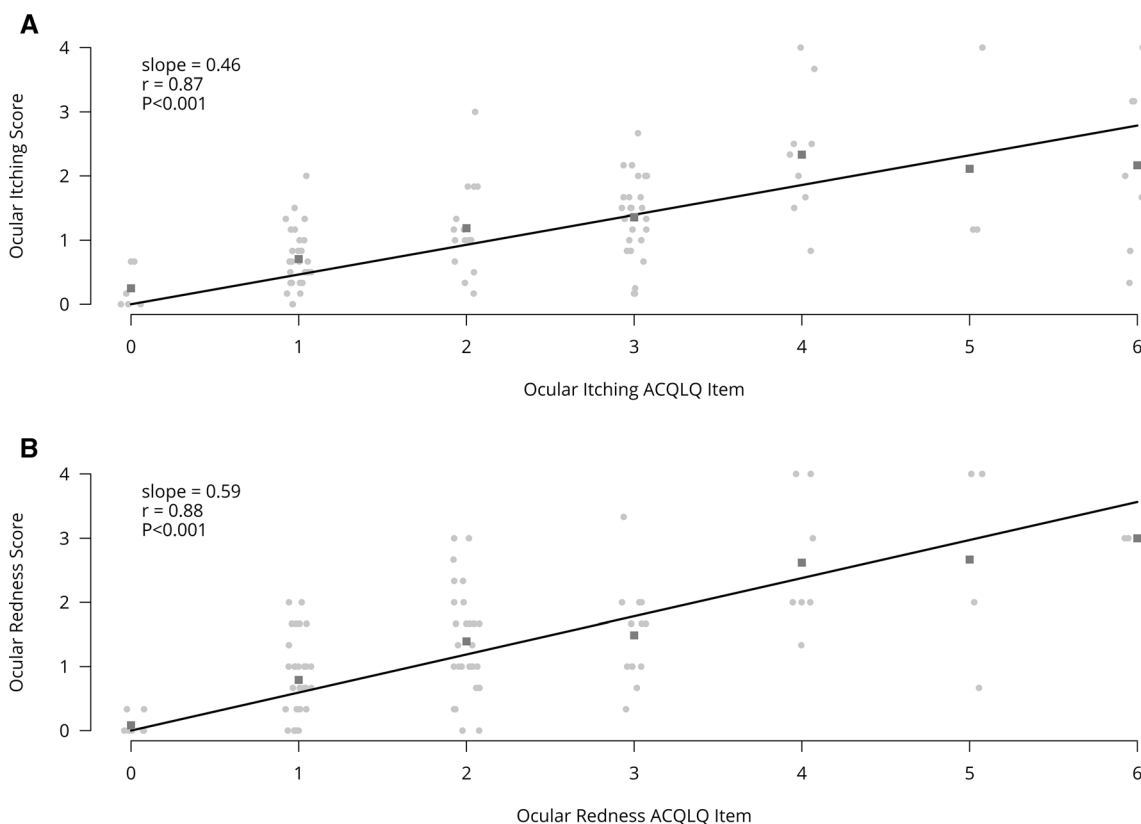


Fig. 4 Relationship of **a** ocular itching and **b** ocular redness scores to quality-of-life scores. For all randomized participants, patient-reported ocular itching and redness scores were plotted relative to Allergic Conjunctivitis

Quality of Life Questionnaire (ACQLQ) items for itching and redness, respectively

Although the estimation of meaningful clinical thresholds is influenced by response options, patient population, number of items, assessment type, frequency of test administration, and other factors, the 0.5-unit value suggested for meaningful within-patient change by the anchor-based techniques described is consistent with that of other scales. Using anchor-based techniques, Zisapel and Nir noted that a 1-point change on a 5-point scale for sleep quality likely overestimates within-patient relevance thresholds [26]. Meaningful within-patient improvement as a percentage of scale across a variety of ranges was reviewed and prospectively tested using anchor-based techniques with two functional scales, two utility scales, and a performance scale in patients with

cancer and was 4.5% on average, which is equivalent to less than 0.25 points for the ocular itching and redness scales [22].

Meaningful within-patient change estimates the difference that is relevant to individual patients, and is generally larger than clinically relevant between-group differences [21]. With respect to ocular itching, therefore, the within-patient estimate of approximately 0.5 points suggests that the 1-point between-group threshold of clinical relevance that has been typically employed is overly conservative and may substantially underestimate the clinical relevance of drug activity in allergic conjunctivitis trials [12]. Similarly, the 2-point responder analysis demonstrating the clinical relevance of reproxalap in the ALLEVIATE

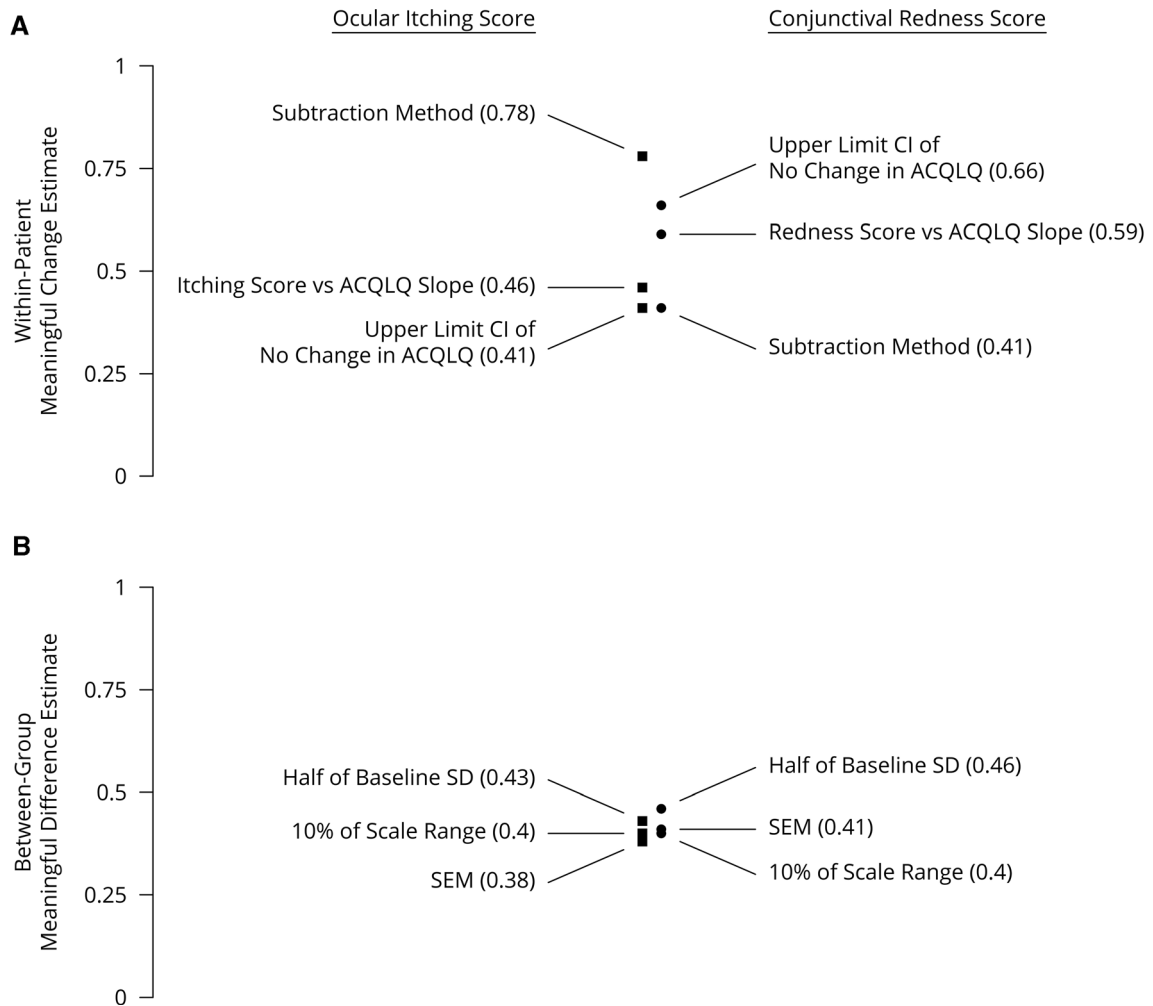


Fig. 5 Threshold estimates for **a** meaningful within-patient change, as assessed by anchor-based analyses, and **b** between-group meaningful difference, as assessed by distribution-based analyses. Squares indicate ocular itching score estimates, and circles indicate ocular redness score estimates. Both ocular itching and redness scores were

reported by patients over a range of 0 (none) to 4 (severe). *ACQLQ* Allergic Conjunctivitis Quality of Life Questionnaire, *SD* standard deviation, *SEM* standard error of the mean

allergic conjunctivitis trial suggests that the average between-group difference in ALLEVIATE during the time frame of the responder analysis (0.4 points) is clinically meaningful and consistent with the data summarized above [9]. Finally, the clinical utility estimates derived from the present trial suggest that the reduction in itching and redness scores presented in Fig. 3 are clinically meaningful.

CONCLUSIONS

This clinical trial found reproxalap to be well tolerated and superior to vehicle in reducing ocular itching on high-pollen days. Additionally, relative to the patient-reported ocular itching and redness scales typically used in allergic conjunctivitis clinical trials, the results from the present trial suggest a new threshold for responder analyses and imply that the typical between-group threshold for clinical

relevance in future clinical trials could be reasonably lowered. Larger trials correlating changes in QOL with changes in patient-reported ocular itching and redness scores are warranted to confirm the clinical relevance threshold findings reported herein.

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Compliance with Ethics Guidelines. The trial (ClinicalTrials.gov, NCT03660878) was performed in the USA in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Patients, the International Council for Harmonisation Guideline on Good Clinical Practice, and all applicable local regulatory requirements and laws. The trial was carried out with approval from an Institutional Review Board (Alpha IRB, San Clemente, CA, USA), informed consent was obtained from the patients, and the research followed Health Insurance Portability and Accountability Act regulations.

Data Availability. The datasets generated during and/or analyzed during the current clinical trial are available from the corresponding author on reasonable request.

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