

REVIEW ARTICLE

Efficacy and safety of reproxalap for the treatment of dry eye disease: a systematic review and meta-analysis

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ABSTRACT

Background: Reproxalap, a reactive aldehyde species inhibitor, has been proposed for dry eye disease (DED), but trial findings are inconsistent, and no quantitative synthesis exists. We assessed the efficacy and safety of reproxalap 0.25% ophthalmic solution versus vehicle in adults with DED.

Methods: PubMed, Web of Science, ClinicalTrials.gov, gray literature, and manufacturer sources were searched through June 2025 (International Prospective Register of Systematic Reviews CRD420251069765; Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020). Two reviewers independently screened, extracted data, and assessed risk of bias. Random- or fixed-effects models were used according to heterogeneity. Standardized mean differences (SMDs), mean differences (MDs), and risk ratios (RRs) were pooled with 95% confidence intervals (CIs). Certainty was assessed using Grading of Recommendations, Assessment, Development, and Evaluations.

Results: Eight randomized controlled trials (1,436 participants) were included. Reproxalap did not significantly improve ocular dryness (SMD, -0.07; 95% CI, -0.24 to 0.10; $I^2 = 47\%$; $p = 0.43$) or conjunctival redness (MD, -0.06; 95% CI, -0.19 to 0.07; $I^2 = 73\%$; $p = 0.36$; random-effects). Tear production significantly increased (MD, 2.20 mm; 95% CI, 1.45-2.94; $I^2 = 0\%$; $p < 0.0001$). Adverse events (AEs) were more frequent with reproxalap (overall RR, 16.30; 95% CI, 4.46-59.55; $I^2 = 94\%$; $p < 0.0001$), although the magnitude of excess varied by study setting: chamber trials showed a larger effect (RR, 25.98; 95% CI, 15.17-44.48; $I^2 = 0\%$), while field trials showed a smaller but still elevated risk (RR, 6.01; 95% CI, 1.25-28.85). Certainty was moderate for AEs and tear production, and very low for dryness and redness.

Conclusion: Reproxalap 0.25% significantly increased tear production by 2.2 mm, although its clinical relevance is uncertain given the ≥ 10 mm responder threshold. No benefit was observed for ocular dryness or conjunctival redness. Larger, well-designed field trials are needed to confirm clinical benefit.

Keywords: Reproxalap, dry eye disease, reactive aldehyde species, ocular surface inflammation, meta-analysis, systematic review.

Introduction

Dry eye disease (DED) represents a significant clinical challenge. It is a common, multifactorial condition defined not only by ocular discomfort and visual disturbance but also by its profound negative impact on an individual's quality of life [1,2]. The prevalence of DED has shown a rising trend, affecting millions of adults globally and necessitating effective therapeutic options to alleviate its burdensome symptoms [1]. The etiology of DED is complex and involves inflammation, meibomian gland dysfunction, and reduced tear production [2]. Reproxalap, a novel reactive aldehyde species (RASP)

inhibitor, has been proposed as a potential treatment for DED, with a mechanism of action aimed at reducing the inflammation and oxidative stress associated with

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46	the disease [3]. Several clinical trials have investigated	are provided in Electronic Supplementary Material 1	103
47	the early onset and activity of reproxalap on signs and	(ESM_1).	104
48	symptoms of DED, though findings across trials have		
49	been inconsistent [4].		
50	Despite this, the clinical community is faced with conflicting	Eligibility criteria	105
51	evidence. The outcomes from various randomized	Studies were included if they were RCTs, including parallel-	106
52	controlled trials (RCTs) have been inconsistent, creating	group and crossover designs, that evaluated topically	107
53	clinical uncertainty about the drug's true therapeutic value	administered reproxalap 0.25% ophthalmic solution	108
54	and necessitating a systematic review to resolve these	compared to a vehicle control. Eligible studies enrolled	109
55	discrepancies. While narrative reviews have summarized	adults aged 18 years or older with a clinical diagnosis of	110
56	the available evidence [5], no prior systematic review and	DED. Both published and unpublished trials initiated or	111
57	meta-analysis has quantitatively assessed the efficacy and	published after January 1, 2020, were considered.	112
58	safety of reproxalap 0.25% for DED. Moreover, while		
59	broader systematic reviews on pharmaceutical treatments	Selection process	113
60	for DED exist [6], a focused meta-analysis on reproxalap is	All identified records were imported into the Rayyan	114
61	essential to provide a clear, evidence-based summary. Such	systematic review software for management [9]. Two	115
62	an analysis is critical not only to provide a pooled estimate	review authors independently screened the titles and	116
63	of treatment effect but also to mitigate potential publication	abstracts of all records, followed by a full-text review	117
64	bias by systematically integrating evidence from all eligible	of potentially eligible reports. Any disagreements	118
65	RCTs, irrespective of their publication status.	between reviewers were resolved through discussion and	119
66	Therefore, the objective of this systematic review	consensus.	120
67	and meta-analysis is to systematically summarize the		
68	efficacy and safety of reproxalap 0.25% ophthalmic	Data collection and synthesis	121
69	solution compared to vehicle for improving the signs	Two reviewers independently extracted data from each	122
70	and symptoms in adults with DED. Secondary objectives	included study using a standardized data extraction	123
71	include summarizing the safety and tolerability profile	form. Extracted variables included study design, sample	124
72	of reproxalap and separately quantifying the treatment	size, participant characteristics, intervention details,	125
73	effect on validated ocular signs and patient-reported	and outcome measures. For continuous outcomes,	126
74	ocular symptoms.	we extracted the mean change from baseline, SD, and	127
75	Methods	number of participants. When SD was not reported, it	128
76		was calculated from SE or other available statistics using	129
77	Protocol and registration	established formulas. For binary outcomes [e.g., adverse	130
78	This systematic review and meta-analysis was	events (AE)], the number of events and total number of	131
79	conducted in accordance with a pre-specified protocol,	participants in each group were recorded. When three or	132
80	registered in the International Prospective Register of	more studies reported conceptually similar outcomes, a	133
81	Systematic Reviews (PROSPERO; registration no.	quantitative meta-analysis was performed using a fixed-	134
82	CRD420251069765) [7]. This report was prepared	effects or random-effects model according to the degree	135
83	in accordance with the Preferred Reporting Items for	of heterogeneity ("Statistical analysis" Section).	136
84	Systematic Reviews and Meta-Analyses (PRISMA)		
85	2020 statement [8].	For continuous outcomes, we calculated pooled mean	137
86	Information sources and search strategy	differences (MDs), or standardized MDs (SMDs) where	138
87	A systematic literature search was completed in June	trials used differing assessment scales. For binary safety	139
88	2025. The search strategy included the bibliographic	outcomes, pooled effects are reported as risk ratios	140
89	databases PubMed and Web of Science, as well as the	(RRs) with 95% confidence intervals (CIs). Statistical	141
90	ClinicalTrials.gov trial registry. Gray literature sources	heterogeneity was quantified using the <i>I</i> ² statistic. For	142
91	were also searched, comprising the manufacturer's	the single crossover trial, efficacy data were extracted	143
92	(Aldeyra Therapeutics) corporate website and press	from the first treatment period only, whereas AEs were	144
93	releases, trial registry records on ClinicalTrials.gov, and	extracted from both periods ("Statistical analysis"	145
94	the reference lists of included studies. A systematic search	Section).	146
95	of PubMed was conducted using the following strategy:		
96	(reproxalap[tiab] OR ALD-4031[tiab]) AND	Risk of bias and certainty assessment	147
97	("Keratoconjunctivitis Sicca"[Mesh] OR "dry eye"[tiab]	The risk of bias in each included RCT was assessed	148
98	OR "dry eyes"[tiab] OR "keratoconjunctivitis sicca"[tiab])	independently by two reviewers using the Cochrane Risk	149
99	AND ("randomized controlled trial"[pt] OR "controlled	of Bias 2 (RoB 2) tool [10]. The overall certainty of the	150
100	clinical trial"[pt] OR randomized[tiab] OR placebo[tiab]	body of evidence for the primary outcomes was assessed	151
101	OR trial[tiab]). No date or language restrictions were	using the GRADE (Grading of Recommendations,	152
102	applied. The last search was conducted on 30 June	Assessment, Development, and Evaluations) framework.	153
	2025. The complete search strategies for all databases	Statistical analysis	154
		Meta-analysis was conducted using RevMan (version	155
		5.4.1; The Cochrane Collaboration, London, UK) [11].	156

157	For continuous outcomes, we calculated pooled MDs	a formal quantitative assessment with funnel plots was not	216
158	when all included trials used the same assessment scale	performed, as such tests are considered unreliable with	217
159	(conjunctival redness, 0-4; Schirmer test, mm). For ocular	a limited number of studies. To proactively mitigate the	218
160	dryness, which was measured using different scales	potential impact of publication bias, our search strategy	219
161	(0-4 and 100 mm visual analog scale), we calculated	was designed to be as comprehensive as feasible.	220
162	pooled SMDs. For the binary safety outcome (AEs),		
163	we calculated pooled RRs with 95% CIs. Statistical	Results	221
164	significance was set at a two-sided $p < 0.05$.		
165	We assessed statistical heterogeneity using the chi-	Study selection	222
166	square test (with a significance threshold of $p < 0.10$)	A total of 22 records were identified: 15 from PubMed	223
167	and quantified it using the I^2 statistic, where I^2 values of	and Web of Science, six from ClinicalTrials.gov, and one	224
168	25%, 50%, and 75% represented low, moderate, and high	from a published report. After removing eight duplicate	225
169	heterogeneity, respectively. Fixed-effects models were	records, 14 unique records proceeded to title and abstract	226
170	used for outcomes with low or moderate heterogeneity (I^2	screening, where four were excluded. The remaining	227
171	$< 50\%$). Random-effects models (DerSimonian-Laird)	10 full-text reports were retrieved and assessed for	228
172	were used as the primary analysis for outcomes with	eligibility. Of these, two were excluded, one for using the	229
173	substantial heterogeneity ($I^2 \geq 50\%$), as recommended	incorrect intervention concentration and one for utilizing	230
174	by the Cochrane Handbook for Systematic Reviews	an inappropriate comparator [3,12].	231
175	of Interventions. For outcomes analyzed with random-	Finally, eight studies met the inclusion criteria and were	232
176	effects models, we also performed fixed-effects sensitivity	incorporated into the systematic review, in accordance with	233
177	analyses to assess the robustness of the pooled estimates;	the PRISMA 2020 flow diagram guidelines (Figure 1).	234
178	these forest plots were added to the Supplementary		
179	Materials (ESM_2).	Study characteristics	235
180	The single crossover trial identified (Garg et al. [18]) was	Descriptive data of the included studies	236
181	not analyzed using the two periods as independent groups,	Eight RCTs involving 1,436 participants were included.	237
182	as this would violate the assumption of independence and	Across the eight trials, ranging from Phase 2-3, reproxalap	238
183	artificially inflate the sample size (unit-of-analysis error).	ophthalmic solution was consistently evaluated in	239
184	Instead, we extracted and analyzed data from the first	randomized, double-masked, vehicle-controlled settings.	240
185	treatment period only. This approach was chosen a priori	These included multicenter field studies, single-center	241
186	to eliminate the potential for carry-over effects and to	crossover models, and CAE challenges. The sample	242
187	ensure independence of observations. We acknowledge	sizes varied from 63 to 361 patients, with treatment	243
188	that this approach may underestimate the precision of	durations spanning from 2 days (in the run-in and	244
189	that trial's contribution relative to a full paired analysis,	chamber studies) to 12 weeks (in the RENEW trial;	245
190	but it avoids the statistical invalidity of treating repeated	ClinicalTrials.gov NCT03879863 and NCT04674358)	246
191	measurements as independent. AEs, however, were	[13]. Despite differences in study design, individual	247
192	pooled across both treatment periods, as safety outcomes	trial reports described improvements in tear production,	248
193	are counted per treatment exposure rather than per	ocular dryness, and redness with reproxalap. Chamber-	249
194	participant; this approach maximizes the capture of	based trials generally reported larger effects, while the	250
195	safety data.	real-world field trial did not achieve its pre-specified	251
196	For outcomes with sufficient data, we performed	primary endpoint. These descriptive observations should	252
197	prespecified subgroup analyses by study design to	be interpreted in the context of the pooled analyses below,	253
198	investigate potential effect modification. Studies were	which formally assess between-study heterogeneity and	254
199	classified as:	risk of bias (Table 1). Efficacy and safety data as reported	255
200	• Chamber studies: Trials conducted in controlled	by the individual trial authors are provided in ESM_3	256
201	adverse environment (CAE) chambers, typically	(Table S1).	257
202	involving short-term (1-2 days) exposure to low-	For Garg et al. [18], a crossover trial, efficacy outcomes	258
203	humidity conditions.	were analyzed using first-period data only ($n = 57$) to	259
204	• Field studies: Trials conducted in real-world, routine	avoid unit-of-analysis error, while AEs were pooled	260
205	clinical settings over longer durations (up to 12	across both periods ($n = 126$ observations) to maximize	261
206	weeks).	safety data capture.	262
207	Subgroup differences were assessed using the interaction	Risk of bias in included studies	263
208	chi-square test, with a significance threshold of $p <$	Figure 2 presents the risk of bias assessment of the	264
209	0.10. Leave-one-out sensitivity analyses assessed the	eight included RCTs using the RoB 2 tool. With	265
210	robustness of pooled estimates.	the exception of the Field Trial, which was rated at	266
211	Assessment of reporting biases	high risk across all domains, randomization (D1)	267
212	We planned to assess the risk of publication bias by	and outcome measurement (D4) were rated at low	268
213	visually inspecting funnel plots for asymmetry for	risk throughout, indicating robust trial conduct and	269
214	any outcome meta-analyzed with 10 or more studies.	effective blinding. There were only occasional concerns	270
215	However, as no outcome included more than eight studies,		

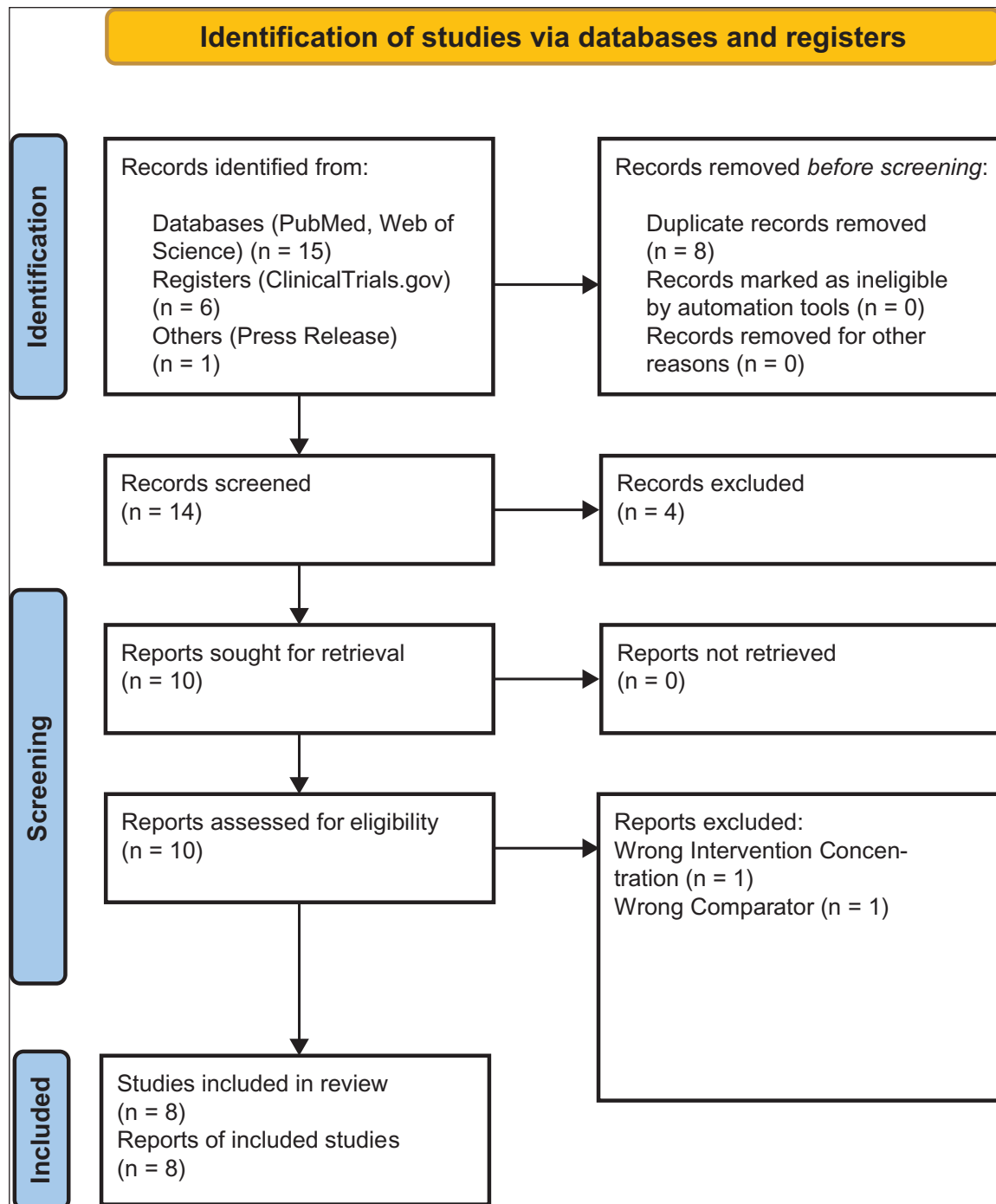


Figure 1. PRISMA 2020 flow diagram of the study identification, screening, and selection process. Adapted from the PRISMA 2020 flow diagram template [8], available under a CC BY 4.0 license.

271 regarding deviations from the intended interventions
 272 (D2), primarily related to variations in dosing around
 273 controlled adverse exposures compared to the protocol.
 274 The most significant issues arose from missing outcome
 275 data (D3) and selective reporting (D5). This was
 276 particularly evident in the Field Trial, which lacked key
 277 quantitative results and predefined endpoints, leading to
 278 judgments of “some concerns” or “high risk.” Overall,
 279 three trials were judged at low risk of bias, four raised
 280 some concerns, and one was at high risk.

Results of individual studies and syntheses

Ocular dryness

Pooled across three trials (529 participants),
 reproxalap 0.25% did not differ significantly from
 vehicle for ocular dryness symptoms (SMD, -0.07;
 95% CI, -0.24 to 0.10; $p = 0.43$; $I^2 = 47\%$; $p = 0.15$).
 Subgroup estimates were similarly null in chamber
 studies (SMD, -0.09; 95% CI, -0.40 to 0.23; $p = 0.59$)

Table 1. Summary of reproxalap clinical trials in DED.

First author, year	Study design and setting	Number of patients	The mean (SD) age (years)	Gender M/F (n)	Intervention Treatment duration
Clark et al., 2021 [4]	Phase 2b, multicenter, randomized, double-masked, vehicle-controlled at multiple US ophthalmology sites	Total: 200 patients Reproxalap 0.25%: 100 Vehicle: 100	Total: 63.5 (11.4) Reproxalap 0.25%: 62.7 (11.1) Vehicle: 63 (11.7)	Total: 53/147 Reproxalap 0.25%: 25/75 Vehicle: 28/72	Vehicle reproxalap 0.25% ophthalmic solution All patients received one drop per eye, four times daily (QID) for 12 weeks.
The RENEW Trial, 2025 [13]	Phase 3, multicenter at Eye Research Foundation, Newport Beach, CA, USA	Total: 211 Reproxalap 0.25%: 105 Vehicle: 106	All adults ≥ 18 years	56/155 Reproxalap 0.25%: 27/78 Vehicle: 29/77	Interventions: - Reproxalap ophthalmic solution 0.25%, administered four times daily (QID) for 12 weeks ("constant dosing"). - Vehicle comparator (matched with QID dosing). Treatment duration: The total treatment duration is 12 weeks, of QID dosing in the arm.
Chamber Trial, 2025 [14]†	Phase 3 in the United States (Lexington, Massachusetts).	Total: 116 Reproxalap 0.25%: 58 Vehicle: 58	NR	NR	Intervention reproxalap 0.25% ophthalmic solution versus matching vehicle Treatment duration: Single-day chamber challenge - dosing immediately before and during 80-100 minutes low-humidity exposure
Field Trial, 2025 [14]†	Phase 3, randomized, double-masked, vehicle-controlled, parallel-group field trial.	NR	NR	NR	Intervention reproxalap 0.25% ophthalmic solution versus matching vehicle
TRANQUILITY Trial [15]	Phase 2/3 Clinical Trial at multicenter (U.S.)	Total: 327 Reproxalap 0.25%: 164 Vehicle: 163	All adults ≥ 18 years	89/238 Reproxalap 0.25%: 46/118 Vehicle: 43/120	Drug: Reproxalap Ophthalmic Solution (0.25%) administered over two consecutive days (Day 1 pre-dry eye chamber and Day 2 dry eye chamber assessment). Placebo comparator: Vehicle Ophthalmic Solution administered over two consecutive days.
TRANQUILITY-2 Trial [16]	Phase 3, multicenter U.S. trial	Total: 361 Reproxalap 0.25%: 181 Vehicle: 180	Reproxalap 0.25%: 64.2 (12.2) Vehicle: 61.9 (12.9)	112/249 Reproxalap 0.25%: 58/123 Vehicle: 54/126	Interventions: • reproxalap 0.25% ophthalmic solution administered in 7 doses over two consecutive days. • Matched vehicle solution given with the same dosing schedule. Treatment duration: 2 days (Day 1: four doses plus pre-/post-Schirmer tests; Day 2: four doses around a 90-minute dry-eye chamber exposure).
Phase 2 Trial, 2025 [17]	Phase 2, single-center (Andover Eye Associates, MA, USA)	Total: 158 Reproxalap 0.25%: 80 Vehicle: 78	All adults ≥ 18 years	44/114 Reproxalap 0.25%: 21/59 Vehicle: 23/55	Intervention: reproxalap 0.25% ophthalmic solution, administered in 7 doses over 2 consecutive days. Comparator: Vehicle ophthalmic solution, with the same dosing schedule. Treatment duration: 2 days, including 4 drops on Day 1 before and after the Schirmer test, and 4 drops on Day 2 around a 90-minute chamber challenge.
Garg et al., 2025 [18]	Vehicle-controlled, randomized-sequence, double-masked, 2-period crossover trial; performed at a single center in Canada	63 patients were randomized and treated. (57 patients completed both periods)	NR	NR	Intervention: Reproxalap 0.25% ophthalmic solution versus matched vehicle. Dosing regimen: 4 doses on the pre-chamber day (over ~4 hours), followed by 1 dose 5 minutes before the 90-minute chamber entry, and 1 dose 45 minutes after chamber entry. Treatment Duration per period: 2 days (Day 1: pre-chamber dosing; Day 2: chamber dosing). Washout: 7-14 days between the two crossover periods.

NR, not reported. Two trials (Field Trial and Chamber Trial, 2025) did not disclose participant-level demographic data or quantitative outcome data. These trials are marked with a dagger (†) and were excluded from all meta-analyses due to insufficient reported data. The total $n = 1,436$ is derived from the seven trials that reported enrollment; the Field Trial did not report sample size.

and field studies (SMD, -0.06 ; 95% CI, -0.26 to 0.14 ; $p = 0.56$), with no significant subgroup difference ($p = 0.89$). The field subgroup was internally inconsistent ($I^2 = 73\%$; $p = 0.05$), with Clark et al. [4] favoring reproxalap and the RENEW trial favoring vehicle (Figure 3).

Conjunctival redness

The pooled analysis of three trials ($n = 521$) showed no significant difference between reproxalap 0.25% and vehicle for conjunctival redness (MD: -0.06 , 95% CI: -0.19 to 0.07 ; $p = 0.36$) using a random-effects model due to substantial heterogeneity ($I^2 = 73\%$; $p =$

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Garg et al., 2026	+	+	+	+	+	+
	RENEW Trial, 2025	+	+	-	+	-	-
	TRANQUILITY Trial, 2025	+	+	-	+	-	-
	TRANQUILITY-2 Trial, 2025	+	+	+	+	+	+
	Phase 2 Trial, 2025	+	+	+	+	+	+
	Chamber Trial, 2025	+	+	+	+	-	-
	Field Trial, 2025	X	X	X	X	X	X
	Clark et al., 2021	+	-	-	+	-	-
		Domains: D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.					Judgement X High - Some concerns + Low

Figure 2. Risk of bias assessment of the eight included RCTs using the Cochrane RoB 2 tool. Green circles denote low risk, yellow circles some concerns, and red circles high risk. D1 randomization process, D2 deviations from intended interventions, D3 missing outcome data, D4 measurement of the outcome, D5 selection of the reported result. For the Garg et al. crossover trial [18], the additional domain DS (bias arising from period and carry-over effects), not shown in the figure, was rated low risk due to a 7- to 14-day washout period that substantially exceeds the expected half-life of an ophthalmic solution.

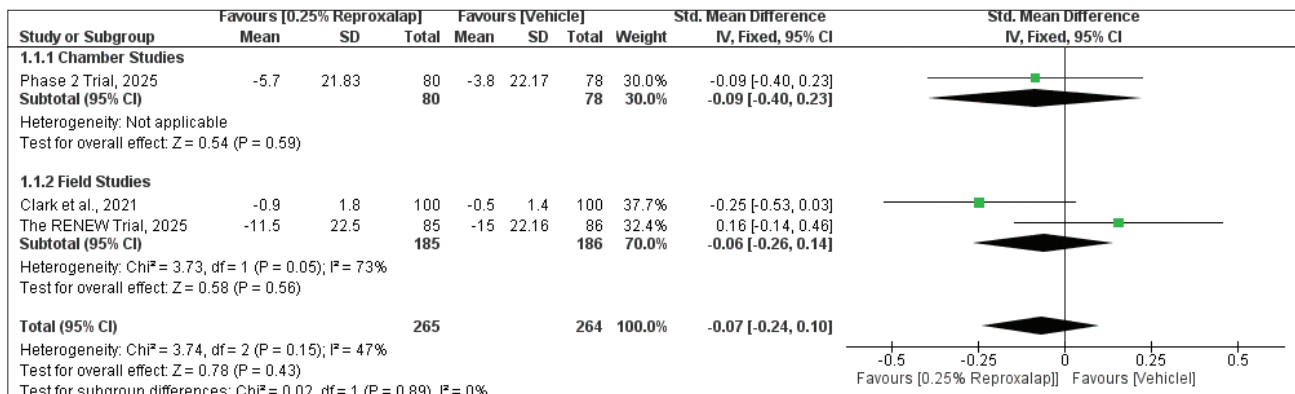


Figure 3. Forest plot of reproxalap 0.25% versus vehicle for ocular dryness score, subgrouped by study design (chamber vs. field trials). Effects are SMDs with 95% CIs under a fixed-effects model.

0.03) (Figure 4). The neutral overall estimate masks considerable inconsistency in the direction of effect: the TRANQUILITY trial, contributing 45.2% of the weight, favored vehicle (MD: 0.03, 95% CI: -0.04 to 0.09), while the Phase 2 trial (MD: -0.12, 95% CI: -0.21 to -0.02) and the Garg crossover trial (MD: -0.17, 95% CI: -0.44 to 0.10) both favored reproxalap. This conflicting pattern, with the largest trial pointing toward harm while smaller trials suggest benefit,

precludes a definitive conclusion and underscores that the null finding is not a precise estimate of no effect but rather an average of disagreeing estimates. The random-effects model was applied to account for between-study variance; however, the CI remains wide and includes both clinically meaningful benefit and harm, indicating low precision. Overall, the current evidence does not establish a consistent benefit of reproxalap for reducing conjunctival redness.

The pooled analysis of five trials ($n = 1,082$) demonstrated that reproxalap 0.25% significantly increased Schirmer test scores compared with vehicle under a fixed-effects model (MD, 2.20 mm; 95% CI, 1.45-2.94; $p < 0.0001$), with no detectable heterogeneity across studies ($I^2 = 0\%$; $p = 0.97$) (Figure 5). The effect was consistent and statistically significant within the chamber subgroup, which comprised four trials and 83.7% of the total weight (MD, 2.31 mm; 95% CI, 1.50-3.13; $p < 0.00001$; $I^2 = 0\%$). In the single field trial contributing to this outcome, the estimate was smaller and did not reach statistical significance (MD, 1.60 mm; 95% CI, -0.25 to 3.45; $p = 0.09$). The test for subgroup differences was not significant ($p = 0.49$), indicating that the observed attenuation in the field setting did not represent a statistically meaningful interaction between study design and treatment effect. However, the point estimate in routine clinical conditions was less than half that observed in the CAE, and the CI included the null. The clinical relevance of a mean increase of ~2 mm remains uncertain, particularly given that the TRANQUILITY-2 trial defined a ≥ 10 mm Schirmer increase as a clinically meaningful responder threshold, a magnitude substantially larger than the observed pooled MD. Overall, these findings confirm a consistent secretory effect under controlled chamber conditions but do not establish a clinically meaningful benefit under routine field conditions. A leave-one-out sensitivity analysis was not informative for this outcome, as heterogeneity was already absent ($I^2 = 0\%$).

Pooled analysis of six trials ($n = 1,381$) showed that reproxalap 0.25% was associated with a significantly higher risk of AEs compared with vehicle (overall test $Z = 4.22$; $p < 0.0001$), with substantial heterogeneity across studies ($I^2 = 94\%$, $\text{Tau}^2 = 2.36$) (Figure 6). Overall, the pooled random-effects RR across all six trials was 16.30 (95% CI, 4.46-59.55), reflecting substantial uncertainty from the marked between-study heterogeneity. This heterogeneity was partly explained by study setting. In the four chamber-based trials, the pooled RR was 25.98 (95% CI, 15.17-44.48) with no heterogeneity ($I^2 = 0\%$), reflecting a large and consistent increase in AE reporting in controlled environmental settings. The two field trials yielded a markedly lower pooled estimate of 6.01 (95% CI, 1.25-28.85), although with considerable heterogeneity ($I^2 = 94\%$), driven primarily by the Clark trial (RR, 3.03) compared with the RENEW trial (RR, 12.69). The test for subgroup differences was not statistically significant ($p = 0.08$), indicating that the observed difference between chamber and field settings may be compatible with chance, despite the fourfold disparity in point estimates. The excess risk was predominantly attributable to mild, transient instillation-site discomfort; the only serious AEs reported were two non-ocular events in a single trial, both judged unrelated or unlikely related to treatment.

Overall, the safety data demonstrate a consistently higher AE burden with reproxalap, particularly in chamber settings, although the magnitude of excess varied considerably between trial designs and the field-based evidence was less consistent.

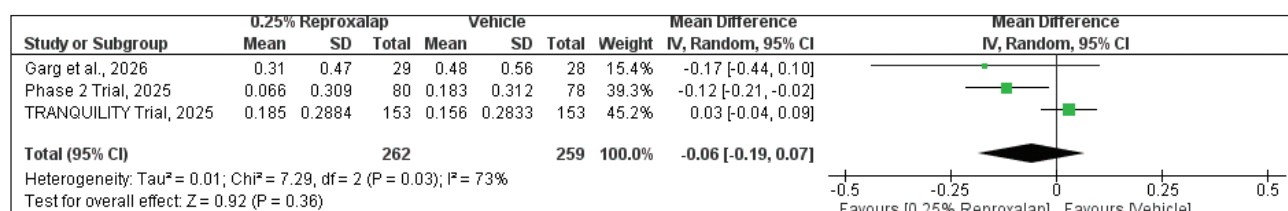


Figure 4. Forest plot of reproxalap 0.25% versus vehicle for conjunctival redness. Effects are MDs on a 0-4 scale with 95% CIs under a random-effects model.

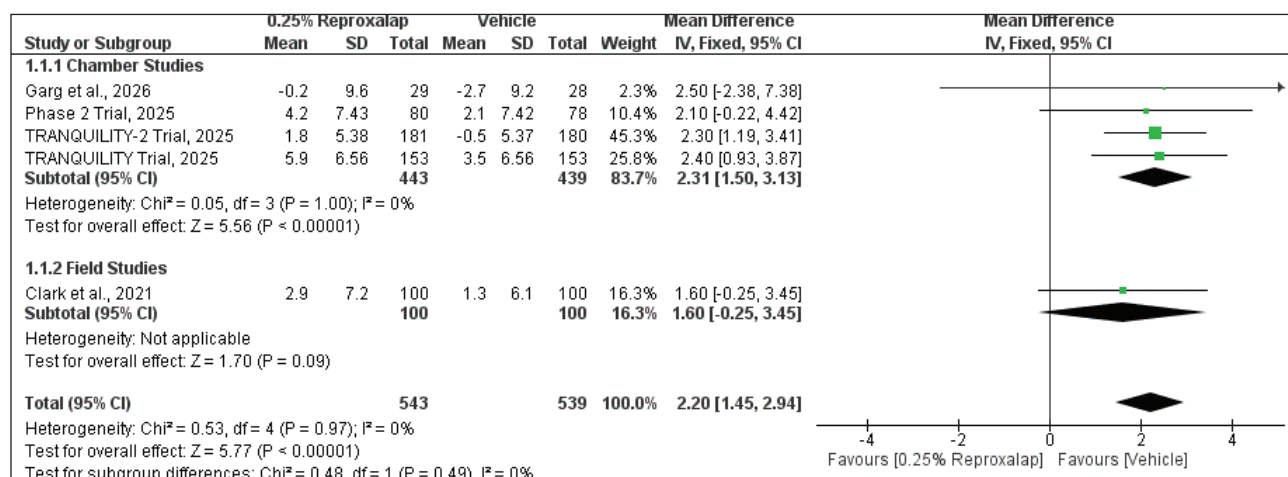


Figure 5. Forest plot of reproxalap 0.25% versus vehicle for tear production measured by the Schirmer test. Effects are MDs in millimeters with 95% CIs under a fixed-effects model.

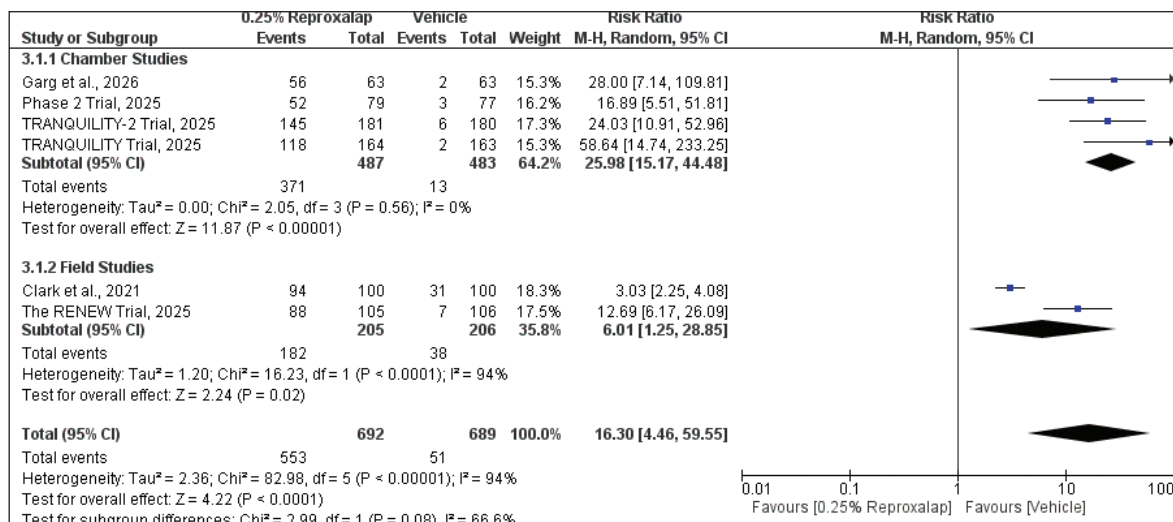


Figure 6. Forest plot of AEs with reproxalap 0.25% versus vehicle, subgrouped by study design (chamber vs. field trials). Effects are RRs with 95% CIs under a random-effects model.

Leave-one-out analysis of conjunctival redness

Leave-one-out sensitivity analysis for conjunctival redness demonstrated that exclusion of the TRANQUILITY trial fundamentally altered the pooled estimate and completely resolved the heterogeneity. With TRANQUILITY removed, the two remaining trials, Garg et al. [18] and the Phase 2 trial, showed consistent effects favoring reproxalap over vehicle, with a pooled MD of -0.12 (95% CI, -0.21 to -0.03 ; $p = 0.008$) and no residual heterogeneity ($P = 0\%$; $p = 0.72$). This stands in marked contrast to the primary analysis, which included TRANQUILITY and yielded a neutral estimate with substantial inconsistency ($P = 73\%$). The TRANQUILITY trial was the only study pointing in the opposite direction, and its large weight in the primary analysis was sufficient to shift the overall estimate toward the null. The sensitivity analysis confirms that the neutral finding in the main meta-analysis is not a robust estimate of a consistent treatment effect but rather an average of conflicting estimates determined largely by a single discordant trial. The statistical significance and elimination of heterogeneity upon its removal indicate that the evidence for conjunctival redness remains fragile and hypothesis-generating at best, rather than confirmatory (ESM_2, Figure S1).

Leave-one-out analysis of AEs

Leave-one-out sensitivity analysis for AEs confirmed Clark et al. [4] as the primary source of the substantial heterogeneity observed in the primary analysis. Excluding this single field trial reduced the overall P from 94% to 15%, with the pooled RR remaining large and statistically significant (RR, 20.67; 95% CI, 12.78-33.43; $p < 0.00001$). The chamber subgroup estimate (RR, 25.98; 95% CI, 15.17-44.48; $P = 0\%$) remained unchanged, while the field subgroup became represented solely by the RENEW trial (RR, 12.69; 95% CI, 6.17-26.09). The test for subgroup differences was no longer statistically significant ($p = 0.12$), indicating that the marked disparity in effect magnitude observed between chamber and field settings in the primary analysis was largely driven by the

presence of Clark et al. [4] rather than a true interaction between study design and treatment-related AE risk. Nevertheless, the field subgroup estimate following exclusion relied on a single remaining trial, which limits the strength of any conclusion regarding AE risk under routine clinical conditions (ESM_2, Figure S2).

Certainty of evidence (GRADE assessment)

According to the GRADE framework, the certainty of evidence was rated as moderate for AEs and tear production, and very low for both ocular dryness and conjunctival redness (Table 2). Certainty for AEs was downgraded one level for imprecision, as the random-effects model — necessitated by substantial heterogeneity ($P = 94\%$; $\tau^2 = 2.36$) — produced a wide CI (RR, 16.30; 95% CI, 4.46-59.55); nonetheless, all six trials favored vehicle and every individual CI excluded the null, supporting a genuine and substantial safety signal despite the imprecision of the pooled estimate. Evidence for tear production was downgraded one level for indirectness, as four of the five contributing trials, carrying 83.7% of the weight, measured Schirmer scores during a 1-2 day CAE exposure rather than under routine conditions; precision and consistency were otherwise excellent ($P = 0\%$). Evidence for ocular dryness was downgraded for risk of bias, inconsistency, and imprecision: the two trials carrying 70.1% of the weight raised “some concerns” on the RoB 2 tool for a patient-reported outcome, the two field trials produced effects in opposite directions (SMD, -0.25 and 0.16 ; $P = 73\%$ within the subgroup), and the pooled CI spans both appreciable benefit and appreciable harm at a sample size below the optimal information size. Evidence for conjunctival redness was downgraded for risk of bias, inconsistency, indirectness, and imprecision, as the trial carrying 45.2% of the weight raised “some concerns” and the direction of effect conflicted across trials ($P = 73\%$), all measurements were obtained during a 90-minute chamber exposure with no field-based data available, and the CI includes both benefit and harm. Because fewer than 10 trials contributed to any outcome, funnel-plot assessment

Table 2. GRADE summary of findings.

Summary of findings for reproxalap 0.25% ophthalmic solution versus vehicle for patients with DED							
Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Vehicle	Reproxalap 0.25% ophthalmic solution	Difference		
Reproxalap's AEs	1,381 (6 RCTs)	RR = 16.30 (4.46-59.55)	74 per 1,000	1,000 per 1,000 (330-1,000)	1,000 more per 1,000 (from 256 more to 1,000 more)	⊕⊕⊕○ Moderate ^{a,b,c}	
Ocular dryness symptom score Follow-up: range 2 days to 12 weeks	529 (3 RCTs)	-	-	-	-0.07 (-0.24 to 0.1)	⊕○○○ Very low ^{d,e,f}	
Conjunctival redness	521 (3 RCTs)	-	-	-	-0.06 (-0.19 to 0.07)	⊕○○○ Very low ^{g,h,i,j}	
Tear production	1,082 (5 RCTs)	-	-	-	2.2 (1.45-2.94)	⊕⊕⊕○ Moderate ^{c,k}	

was not undertaken; instead, trial registries, sponsor communications, and gray literature were deliberately searched to capture unpublished evidence, and no outcome was downgraded for publication bias on this basis.

^aAlthough $P = 94\%$ indicates substantial statistical heterogeneity, this variation is partly explained by study setting (chamber vs. field trials) and reflects magnitude rather than direction: all six trials favored vehicle and the smallest RR (3.03) remains a large excess.

^bWide CI (RR, 16.30; 95% CI, 4.46-59.55) under the random-effects model, reflecting substantial imprecision in the magnitude of effect. Absolute effects are capped at 1,000 per 1,000, as the pooled RR applied to the vehicle risk exceeds 100% owing to between-trial heterogeneity.

^cThe search deliberately included trial registries, sponsor communications and gray literature to capture unpublished evidence; funnel-plot assessment was not undertaken as fewer than ten trials contributed.

^dThe two trials carrying 70.1% of the weight raised “some concerns” on the RoB 2 tool in domains 2, 3 and 5, and the outcome is patient-reported.

^eThe two field trials gave effects in opposite directions (SMD, -0.25 and 0.16), with $P = 73\%$ within that subgroup and 47% overall.

^fThe CI spans both appreciable benefit and appreciable harm ($p = 0.43$), and $n = 529$ does not meet the optimal information size.

^gThe trial carrying 45.2% of the weight raised “some concerns” in domains 3 and 5 of the RoB 2 tool.

^h $P = 73\%$ with conflicting directions across trials; leave-one-out analysis showed the pooled estimate was determined by a single trial, becoming significant (MD, -0.12; 95% CI, -0.21 to -0.03; $p = 0.008$; $P = 0\%$) once excluded.

ⁱAll three contributing trials measured conjunctival redness during a CAE exposure of up to 90 minutes; no field-based data were available for this outcome.

^jThe CI includes both benefit and harm (MD, -0.06; 95% CI, -0.19 to 0.07; $p = 0.36$) and $n = 521$ does not meet the optimal information size.

^kFour of the five trials, carrying 83.7% of the weight, measured tear production during a 1-2 day CAE exposure rather than under routine conditions. The single 12-week field trial gave a smaller, non-significant estimate (1.60 mm, 95% CI, -0.25 to 3.45).

Discussion

In this systematic review and meta-analysis of eight RCTs, we found that reproxalap 0.25% produced a statistically significant improvement in tear production (MD, 2.20 mm; 95% CI, 1.45-2.94; $P = 0\%$; moderate certainty) but no significant benefit for either ocular dryness symptoms (SMD, -0.07; 95% CI, -0.24 to 0.10; $P = 47\%$) or conjunctival redness (MD, -0.06; 95% CI, -0.19 to 0.07; $P = 73\%$; random-effects), both rated very low certainty. The pattern is therefore one of a measurable effect on an objective secretory sign alongside an absence of demonstrable benefit for the patient-reported symptom that matters most to patients, and for the inflammatory sign of ocular redness.

Two features of the efficacy data warrant emphasis. First, the tear production result, although precise and internally consistent, rests almost entirely on chamber-based measurement: the four CAE trials carried 83.7% of the weight and yielded a pooled estimate of 2.31 mm (95% CI, 1.50-3.13), whereas the single 12-week field trial produced a smaller, non-significant estimate of 1.60 mm (95% CI, -0.25 to 3.45). The clinical relevance of a mean increase of ~2 mm remains uncertain. TRANQUILITY-2 defined a ≥ 10 mm Schirmer increase as a clinically meaningful responder threshold, a

526 magnitude substantially larger than the observed pooled
527 MD. While the secretory effect is statistically robust
528 under controlled conditions, it is unclear whether this
529 translates into meaningful symptom relief for patients in
530 routine clinical practice. Future trials should incorporate
531 patient-reported outcomes alongside objective measures
532 to better define the clinical utility of reproxalap.

533 The test for subgroup differences was not significant (p
534 = 0.49), so the two settings cannot be said to disagree,
535 but neither can a benefit under routine conditions
536 be considered established. Second, the null result
537 for conjunctival redness is an average of conflicting
538 estimates rather than a precise estimate of no effect. The
539 Phase 2 trial (MD, -0.12; 95% CI, -0.21 to -0.02) and
540 the Garg crossover trial (MD, -0.17; 95% CI, -0.44
541 to 0.10) both favored reproxalap, while the weight-
542 dominant TRANQUILITY trial pointed in the opposite
543 direction (MD, 0.03; 95% CI, -0.04 to 0.09). Leave-
544 one-out analysis confirmed this trial as the sole source of
545 inconsistency: with it removed, heterogeneity fell from
546 73% to 0%, and the pooled estimate became significant in
547 favor of reproxalap (MD, -0.12; 95% CI, -0.21 to -0.03;
548 $p = 0.008$). The magnitude of that estimate on a 0-4 scale
549 is nonetheless small and of uncertain clinical importance,
550 and a pooled result that becomes statistically significant
551 only on the removal of one trial cannot support a firm
552 conclusion.

553 The safety signal was the most consistent finding in
554 the review. AEs were substantially more frequent with
555 reproxalap (RR, 16.30; 95% CI, 4.46-59.55; 1,381
556 participants), and the pooled estimate was highly
557 heterogeneous ($I^2 = 94\%$; $\text{Tau}^2 = 2.36$), reflecting genuine
558 uncertainty in the magnitude of effect across trial
559 settings; nonetheless, all six trials favored vehicle and
560 every trial-level CI excluded the null. Heterogeneity was
561 attributable almost entirely to Clark et al. [4], the trial
562 with the lowest RR (RR, 3.03); its removal reduced I^2
563 from 94% to 15% and raised the pooled estimate to 20.67
564 (95% CI, 12.78-33.43). The marked difference between
565 chamber trials (RR, 25.98; 95% CI, 15.17-44.48; I^2
566 = 0%) and field trials (RR, 6.01; 95% CI, 1.25-28.85)
567 plausibly reflects more intensive monitoring, shorter
568 recall periods, and immediate post-instillation assessment
569 in controlled settings rather than a true difference in
570 underlying tolerability. Importantly, the excess consisted
571 predominantly of mild, transient instillation-site
572 discomfort, and the only serious AEs reported were two
573 non-ocular events in a single trial, both judged unrelated
574 or unlikely related to treatment. This tolerability profile
575 is consistent with previous literature [19].

576 Our findings for symptoms are consistent with a recent
577 narrative review by Swartz and Powell [5]. However,
578 our analysis builds on that work by providing the first
579 pooled statistical estimates of treatment effect, a formal
580 risk-of-bias assessment, and a GRADE evaluation across
581 the entire body of evidence, including unpublished trials.
582 Mechanistically, reproxalap traps free RASP on the ocular
583 surface, targeting upstream mediators of inflammation
584 rather than individual downstream cytokines [4,5,12].
585 The dissociation we observed between a positive
586 secretory response and unchanged symptom scores is

not unique to this agent, and mirrors the well-recognized
discordance between signs and symptoms in DED.

The primary strength of this review is its rigorous
methodology, including a pre-registered protocol and a
comprehensive search for both published and unpublished
data. The principal limitation is the methodological quality
of the available primary studies. Our risk of bias assessment
identified three trials at low risk of bias, four raising
“Some concerns,” and one at “High risk” due to a lack of
reported data. This pattern, combined with inconsistency
and imprecision in the symptom and redness outcomes, and
with the predominantly chamber-based measurement of
tear production, is what drove the certainty ratings down to
very low and moderate, respectively. The available data did
not permit disaggregation of AEs by treatment-relatedness
or cause of discontinuation, limiting the granularity of the
safety analysis. None of the included trials systematically
stratified participants by DED subtype (evaporative vs.
aqueous-deficient). Patients with greater ocular surface
inflammation may theoretically derive more benefit from
RASP inhibition, and future trials should consider enrolling
phenotype-defined populations to clarify which patients
respond most favorably. The search was limited to PubMed
and Web of Science; Embase and Scopus were not searched
due to access limitations at the time of the review, which
may have resulted in missed studies. However, to mitigate
this, the corporate website of Aldeyra Therapeutics and
ClinicalTrials.gov were systematically searched to capture
all registered and unpublished trials, as reproxalap is a single-
manufacturer drug with a limited and well-documented trial
portfolio. A further contextual limitation is that all included
trials were sponsored by or conducted in collaboration with
Aldeyra Therapeutics, the drug’s manufacturer. This is a
major limitation: industry-sponsored trials are more likely
than independently funded trials to report favorable efficacy
results and conclusions, and selective outcome reporting
cannot be excluded. In the absence of any independently
conducted trial, the pooled efficacy estimates may overstate
the true benefit of reproxalap. Baseline characteristics were
also incompletely reported in the available sources: mean
age was unavailable for the RENEW, TRANQUILITY,
Phase 2, and Garg trials; sex distribution was unavailable
for the Garg trial; and neither the Chamber Trial nor the
Field Trial reported any demographic data. These data
were requested from the sponsor, but no response had been
received at the time of submission. This limits assessment of
the generalizability of our findings and precluded subgroup
analyses by age or sex.

Two identified trials (Chamber Trial 2025 and Field Trial
2025) could not be included in the quantitative synthesis
due to insufficient reporting of outcome data. The absence
of peer-reviewed, independently verifiable data for these
trials limits the comprehensive assessment of reproxalap’s
efficacy and highlights the need for full trial reports to be
made publicly available. Additionally, for the crossover
trial [18], we used first-period data only for efficacy
outcomes; while this approach avoids the unit-of-analysis
error, it may have underestimated the precision of that
trial’s contribution relative to a paired analysis.

For clinicians, our findings indicate that reproxalap
0.25% increases aqueous tear production but has not

648	been shown to relieve the symptom of ocular dryness or	706
649	to reduce conjunctival redness, and that treatment carries	707
650	a high likelihood of transient instillation-site discomfort.	708
651	For researchers, the priority is clear: adequately powered	709
652	field trials of at least 12 weeks' duration, with pre-specified	710
653	and fully reported symptom endpoints, are needed before	711
654	the clinical role of this agent can be defined.	712
655	Conclusion	713
656	Across eight RCTs, reproxalap 0.25% produced a	714
657	statistically significant increase in Schirmer test scores	715
658	compared with vehicle (MD, 2.20 mm; moderate-certainty	716
659	evidence), though the clinical importance of this magnitude	717
660	remains uncertain given that established responder	718
661	thresholds typically require a ≥ 10 mm improvement. No	719
662	significant benefit was demonstrated for ocular dryness	720
663	symptoms or conjunctival redness (very low-certainty	721
664	evidence for both). Moderate-certainty evidence indicates	722
665	a substantially increased incidence of AEs consisting	723
666	predominantly of mild, transient instillation-site discomfort,	724
667	with no treatment-related serious AEs identified. The	725
668	efficacy findings were derived largely from short CAE	726
669	exposures rather than routine conditions, and the redness	727
670	result became statistically significant only after removal of	728
671	a single weight-dominant trial. Taken together, the current	729
672	evidence is insufficient to establish a consistent clinical	730
673	benefit of reproxalap 0.25% across the signs and symptoms	731
674	of DED, and larger, independently verifiable field trials	732
675	with standardized and fully reported outcomes are required.	733
676	Acknowledgment	734
677	Not applicable.	735
678	List of Abbreviations	736
679	AE Adverse event	737
680	CAE Controlled adverse environment	738
681	CI Confidence interval	739
682	DED Dry eye disease	740
683	GRADE Grading of Recommendations, Assessment,	741
684	Development and Evaluations	742
685	MD Mean difference	743
686	PRISMA Preferred Reporting Items for Systematic	744
687	Reviews and Meta-Analyses	745
688	PROSPERO International Prospective Register of	746
689	Systematic Reviews	747
690	RASP Reactive aldehyde species	748
691	RCT Randomized controlled trial	749
692	RoB 2 Cochrane Risk of Bias 2	750
693	RR Risk ratio	751
694	SD Standard deviation	752
695	SE Standard error	753
696	SMD Standardized mean difference	754
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	manuscript editing; manuscript review.	
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	References	
	1. Valdés-Arias D, Locatelli EV, Sepulveda-Beltran PA,	
	Mangwani-Mordani S, Navia JC, Galor A. Recent United	
	States developments in the pharmacological treatment of	
	dry eye disease. <i>Drugs</i> . 2024;84(5):549–63. https://doi.	
	org/10.1007/s40265-024-02031-6	

2. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. 2017;15:334–65. <https://doi.org/10.1016/j.jtos.2017.05.003>
3. Clark D, Sheppard J, Brady TC. A randomized double-masked phase 2a trial to evaluate activity and safety of topical ocular reproxalap, a novel RASP inhibitor, in dry eye disease. *J Ocul Pharmacol Ther*. 2021;37(4):193–9. <https://doi.org/10.1089/jop.2020.0087>
4. Clark D, Tauber J, Sheppard J, Brady TC. Early onset and broad activity of reproxalap in a randomized, double-masked, vehicle-controlled phase 2b trial in dry eye disease. *Am J Ophthalmol*. 2021;226:22–31. <https://doi.org/10.1016/j.ajo.2021.01.011>
5. Swartz T, Powell W. Reproxalap for the treatment of dry eye disease. *touchREV Ophthalmol*. 2023;17:31. <https://doi.org/10.17925/USOR.2023.17.1.31>
6. PROSPERO. A systematic literature review of clinical evidence for key pharmaceutical treatments in dry eye disease. York: Centre for Reviews and Dissemination; 2024 [cited 2025 Jun 23]. CRD42024599506. Available from: <https://www.crd.york.ac.uk/PROSPERO/view/CRD42024599506>.
7. PROSPERO. Efficacy and safety of reproxalap for the treatment of dry eye disease: a systematic review and meta-analysis of randomized controlled trials. York: Centre for Reviews and Dissemination; 2025 [cited 2025 Jun 23]. CRD420251069765. Available from: <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251069765>
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. <https://doi.org/10.1136/bmj.n71>
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210. <https://doi.org/10.1186/s13643-016-0384-4>
10. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. <https://doi.org/10.1136/bmj.l4898>
11. The Cochrane Collaboration. Review Manager (RevMan), Version 5.4.1. London, UK: The Cochrane Collaboration; 2020.
12. McMullin D, Clark D, Cavanagh B, Karpecki P, Brady TC. A post-acute ocular tolerability comparison of topical reproxalap 0.25% and lifitegrast 5% in patients with dry eye disease. *Clin Ophthalmol*. 2021;15:3889–900. <https://doi.org/10.2147/OPTH.S327691>
13. Aldeyra Therapeutics. The RENEW trial: a multi-center, randomized, double-masked, parallel-group, vehicle-controlled, adaptive phase 3 clinical trial. *ClinicalTrials.gov* identifier NCT03879863. 2025 [cited 2025 Jun 23]. Available from: <https://classic.clinicaltrials.gov/ct2/show/NCT03879863>
14. Aldeyra Therapeutics. Aldeyra Therapeutics achieves primary endpoint in phase 3 dry eye disease chamber trial of reproxalap and plans NDA resubmission [press release]. Lexington, MA: Aldeyra Therapeutics; 2025 [cited 2025 Jun 23]. Available from: <https://ir.aldeyra.com/news-releases/news-release-details/aldeyra-therapeutics-achieves-primary-endpoint-phase-3-dry-eye-0>
15. Aldeyra Therapeutics. The TRANQUILITY trial: clinical trial to assess the efficacy and safety in subjects with dry eye disease. *ClinicalTrials.gov* identifier NCT04674358. 2025 [cited 2025 Jun 23]. Available from: <https://classic.clinicaltrials.gov/ct2/show/NCT04674358>
16. Aldeyra Therapeutics. The TRANQUILITY 2 trial: a phase 3 clinical trial to assess the efficacy and safety in subjects with dry eye disease. *ClinicalTrials.gov* identifier NCT05062330. 2025 [cited 2025 Jun 23]. Available from: <https://classic.clinicaltrials.gov/ct2/show/NCT05062330>
17. Aldeyra Therapeutics. A multi-center, randomized, double-masked, parallel design, vehicle-controlled phase 2 clinical trial. *ClinicalTrials.gov* identifier NCT04971031. 2025 [cited 2025 Jun 23]. Available from: <https://classic.clinicaltrials.gov/ct2/show/NCT04971031>
18. Garg S, Donnenfeld E, Sheppard J, Epitropoulos A, Brady TC. Reproxalap improves ocular redness, tear production, and symptoms in a pivotal dry eye disease chamber trial. *Ophthalmol Sci*. 2026;6(1):100938. <https://doi.org/10.1016/j.xops.2025.100938>
19. Elgadi A, Abdalmotalib MM, Noorallah T, Abdelazim E, Mohammed FA. Reproxalap in patients with seasonal allergic conjunctivitis: a systematic review and meta-analysis. *J Ophthalmic Inflamm Infect*. 2025;15(1):39. <https://doi.org/10.1186/s12348-025-00497-3>