

Pooled Safety and Efficacy Analysis From Two 12-Week Reproxalap Dry Eye Disease Trials

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OBJECTIVE

To evaluate the efficacy and safety of reproxalap 0.25% compared with vehicle in subjects with dry eye disease (DED) using pooled data from two 12-week clinical trials

CONCLUSIONS

Reproxalap was safe and well tolerated in this pooled data analysis of two 12-week clinical trials

Ocular dryness and discomfort scores were reduced with reproxalap compared with vehicle as soon as 1 week after beginning treatment

Reproxalap has potential to be an innovative, rapidly acting therapeutic option for patients with DED

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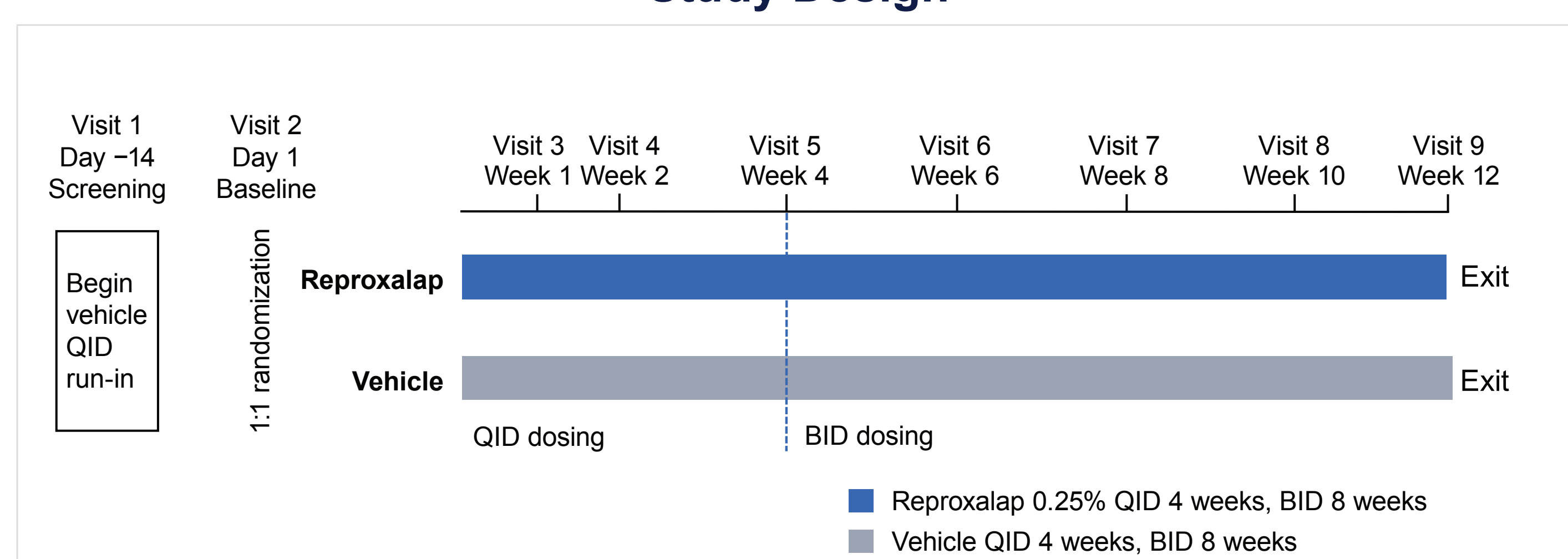
INTRODUCTION

- Dry eye disease (DED) is a prevalent disorder characterized by tear film instability, inflammation, and ocular symptoms¹
- Proinflammatory reactive aldehyde species (RASP) have been implicated in the pathophysiology of DED²
- Levels of the RASP malondialdehyde (MDA) are increased in the tears of patients with DED, and the increase in MDA levels is associated with the severity of DED³
- Reproxalap, a small molecule RASP inhibitor that rapidly and covalently binds RASP² is in development for the treatment of DED
- Reproxalap 0.25% ophthalmic solution is currently under review by the US Food and Drug Administration for treatment of DED

METHODS

- This post hoc analysis used pooled data from 2 multicenter, randomized, double-masked, parallel-group, vehicle-controlled, clinical trials: a phase 2 trial (NCT03916042) and 2 arms of a phase 3 trial (NCT03879863) that were designed identically to the phase 2 trial
- Subjects with DED were randomized 1:1 to receive bilateral reproxalap 0.25% ophthalmic solution or vehicle 4 times daily (QID) for 4 weeks then twice daily (BID) for 8 weeks

Study Design



Screening and baseline assessments included dry eye chamber exposure. BID, twice daily; QID, 4 times daily.

Key Eligibility Criteria for Study Participation

Inclusion Criteria

- Age ≥18 years with history of dry eye ≥6 months before V1
- History of use or desire to use eye drops for dry eye symptoms within 6 months of V1
- OD4SQ score ≥2 for ≥1 symptom at V1 and V2 pre-DEC
- Schirmer test score of 1–10 mm at V1 and V2
- Corneal fluorescein staining score ≥2 in ≥1 region AND tear film break-up time ≤5 s at V1 and V2 pre-DEC
- Total corneal fluorescein staining score ≥4 (sum of inferior, superior, and central regions) at V1 and V2 pre-DEC
- Total lissamine green conjunctival score ≥2 (sum of temporal and nasal regions) at V1 and V2 pre-DEC
- Positive response to DEC at V1 and V2^a
- At V2 pre-DEC, dryness symptom score ≥3 on the OD4SQ AND/OR corneal fluorescein staining score ≥2 in the nasal region in at least 1 qualifying eye

Exclusion Criteria

- Any clinically significant slit-lamp findings, ocular infection, or active ocular inflammation at V1
- Used contact lenses within 7 days or any eye drops within 2 hours of V1
- Laser-assisted in situ keratomileusis (LASIK) surgery within the previous 12 months
- Used ophthalmic cyclosporine or lifitegrast 5.0% ophthalmic solution within 90 days of V1
- Used temporary or permanent punctal plugs within 30 days before V1, or anticipate their use during the study period
- Corrected visual acuity ≥0.7 logMAR per the Early Treatment Diabetic Retinopathy Study (ETDRS) scale in both eyes at V1

^aPositive response defined as ≥1-point increase in fluorescein staining in the inferior region in ≥1 eye post-DEC exposure and ocular discomfort score ≥3 at ≥2 consecutive time points in ≥1 eye during DEC exposure.

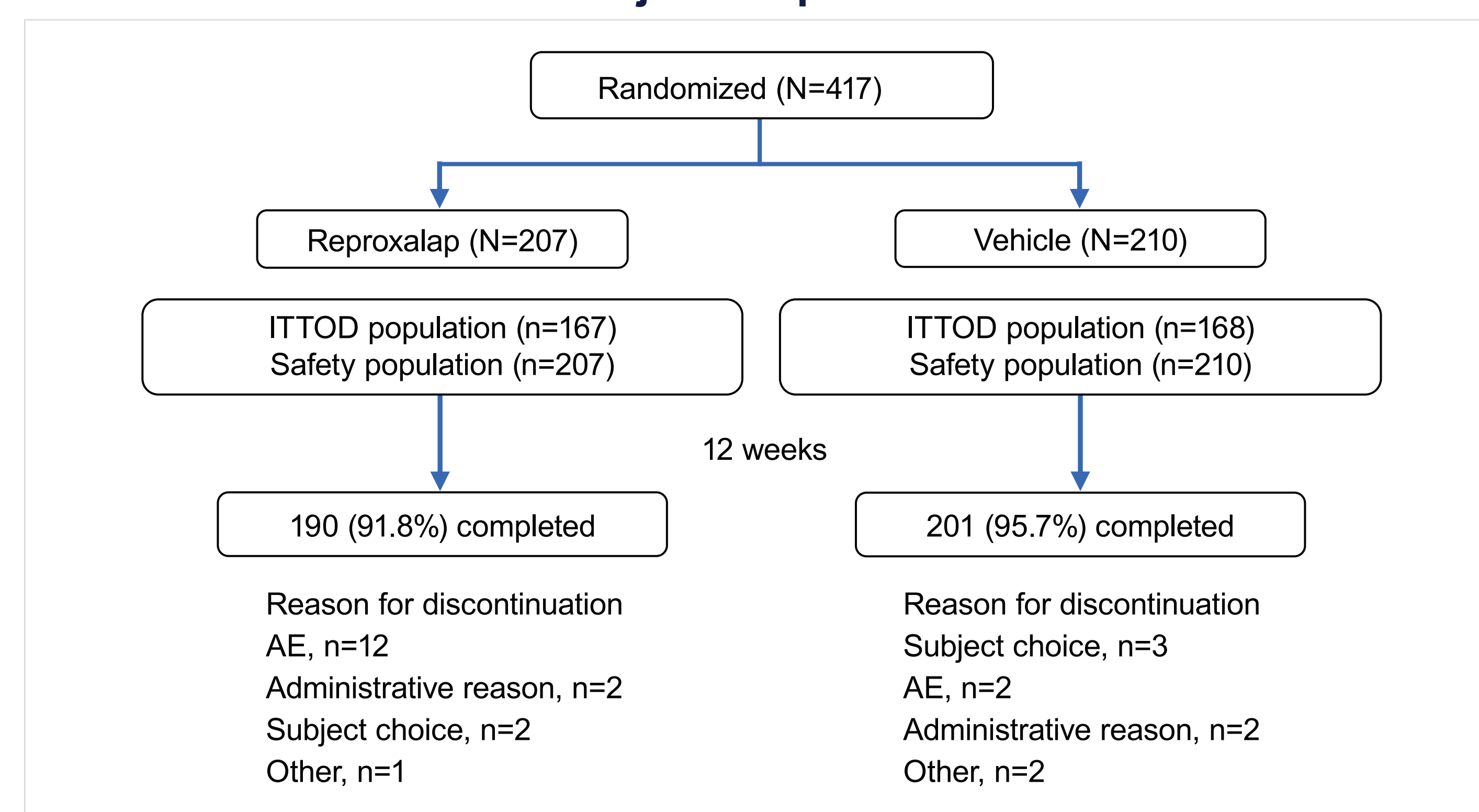
DEC, dry eye chamber; OD4SQ, Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire; V1, visit 1; V2, visit 2.

- If both eyes were eligible, the eye with the worse nasal fluorescein staining score at baseline was selected as the study eye
- Ocular dryness and ocular discomfort were assessed on a visual analog scale (VAS) of 0–100
- Symptoms were evaluated in the intent-to-treat ocular dryness (ITTOD) population (prespecified for primary endpoint analysis in each trial) of all randomized subjects who graded their ocular dryness score as ≥3 (using a 0–5 scale) on the Ora Calibra® Ocular Discomfort & 4-Symptom Questionnaire
- Pooled data ocular dryness and ocular discomfort scores were analyzed using mixed-model repeated measures (MMRM) models with change from baseline (CFB) as the response variable; treatment arm, visit, and the interaction of treatment arm-by-visit as fixed effects; baseline score as a covariate; and subject as a random effect
- Nominal *P* values from the MMRM models are reported
- Safety assessments included adverse events (AEs), slit-lamp biomicroscopy, distance visual acuity measured using an Early Treatment Diabetic Retinopathy Severity (ETDRS) chart, intraocular pressure (IOP), and dilated funduscopy
- Safety parameters were evaluated in the safety population of all randomized subjects who received ≥1 dose of study drug; subjects were analyzed as treated

RESULTS

- A total of 417 subjects were enrolled and randomized to reproxalap or vehicle treatment (QID 4 weeks then BID 8 weeks) across the 2 trials; 335 subjects were included in the ITTOD population
- Study completion rates were high in each treatment group (91.8% with reproxalap, 95.7% with vehicle)
- The rate of discontinuations due to AEs was 5.8% with reproxalap (most commonly because of instillation site irritation) and 1.0% with vehicle

Subject Disposition



AE, adverse event; ITTOD, intent-to-treat ocular dryness.

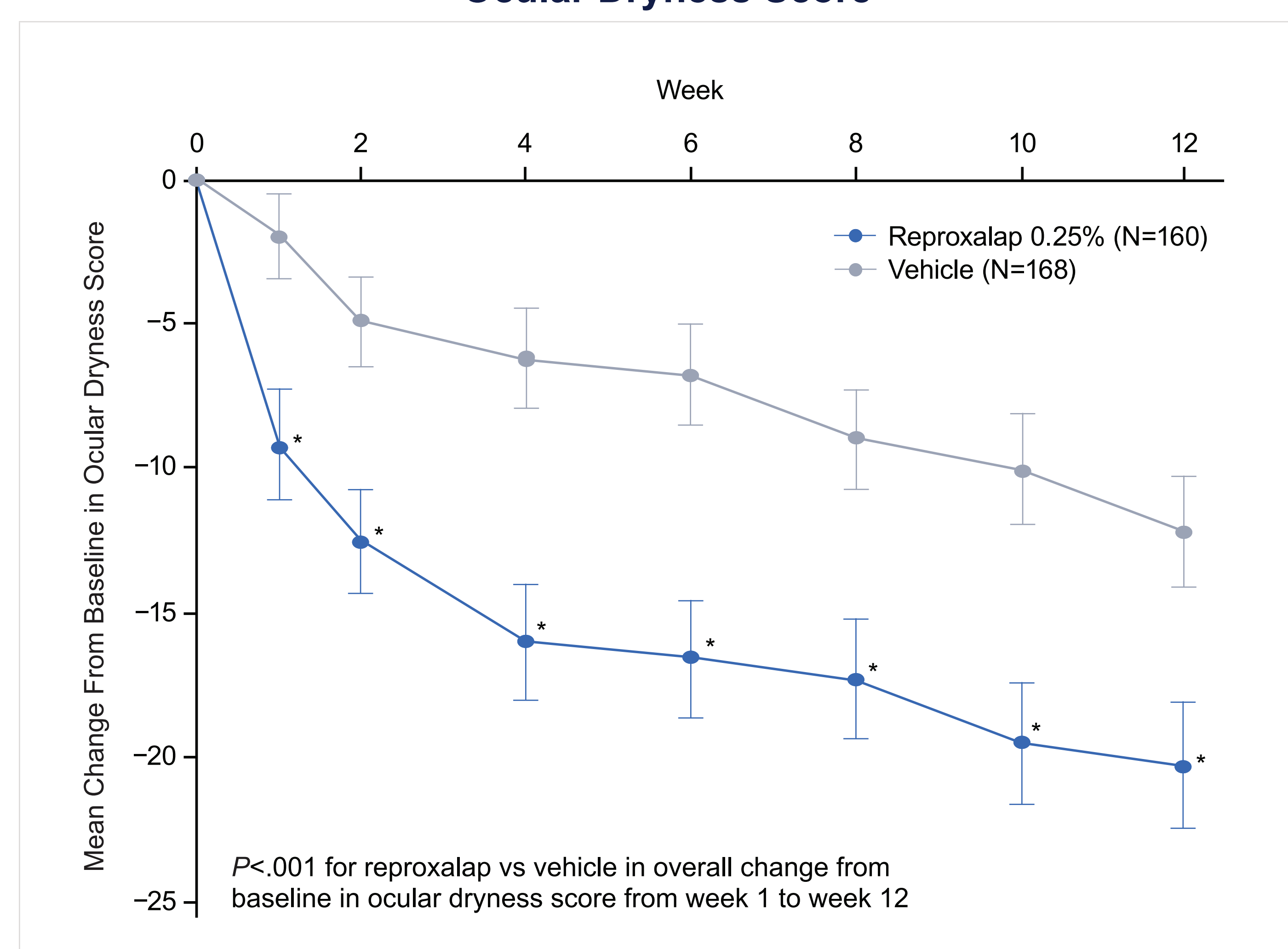
Baseline Characteristics of the ITTOD Study Population

Parameter	Reproxalap N=167	Vehicle N=168
Age, mean (SD), y	65.2 (11.12)	63.3 (11.99)
≥65 y, n (%)	93 (55.7)	84 (50.0)
Female, n (%)	127 (76.0)	123 (73.2)
Race, n (%)		
White	143 (85.6)	140 (83.3)
Black or African American	15 (9.0)	17 (10.1)
Other or multiple	9 (5.4)	11 (6.5)
Ocular dryness score (0–100 VAS), mean (SD)	65.5 (21.24)	64.6 (24.61)
Corneal fluorescein total sum staining score (0–20), mean (SD)	9.3 (1.70)	9.4 (1.87)
Unanesthetized Schirmer test score, mean (SD), mm	5.3 (2.83)	4.9 (3.06)
Corrected visual acuity, mean (SD), logMAR	0.1 (0.14)	0.1 (0.14)

logMAR, logarithm of the minimal angle of resolution; ITTOD, intent-to-treat ocular dryness; VAS, visual analog scale.

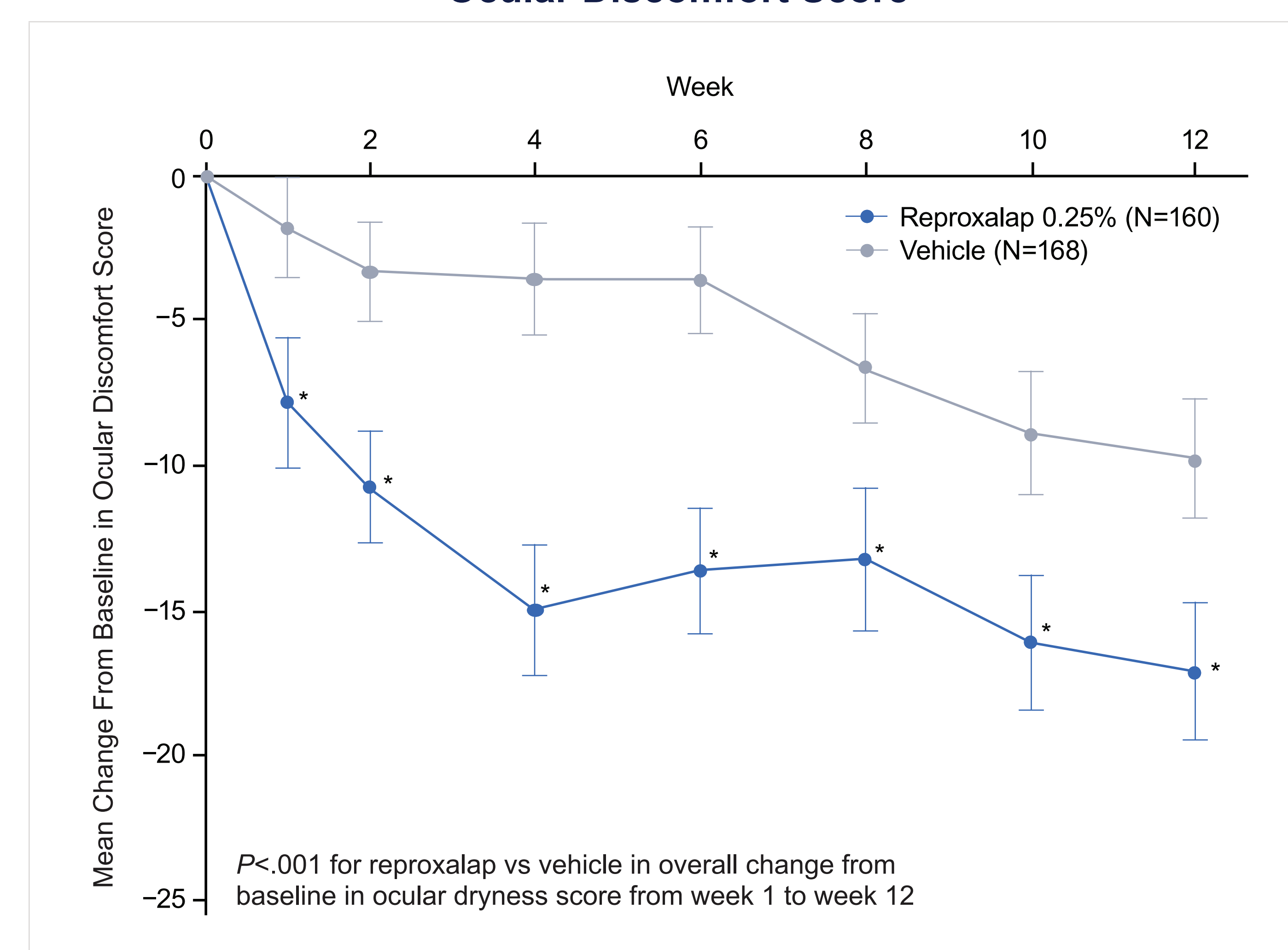
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Ocular Dryness Score



The analysis used observed values for all subjects in the ITTOD population with postbaseline data. Error bars indicate the standard error of the mean. ITTOD, intent-to-treat ocular dryness. **P*<.05 vs vehicle.

Ocular Discomfort Score



The analysis used observed values for all subjects in the ITTOD population with postbaseline data. Error bars indicate the standard error of the mean. ITTOD, intent-to-treat ocular dryness. **P*<.05 vs vehicle.

AEs Reported in ≥1% of Subjects in Either Treatment Group (Safety Population)

AE, n (%)	Reproxalap N=207	Vehicle N=210
Instillation site irritation	108 (52.2)	1 (0.5)
Instillation site pain	74 (35.7)	5 (2.4)
Visual acuity reduced	14 (6.8)	7 (3.3)
Hordeolum	4 (1.9)	0
Vision blurred	4 (1.9)	1 (0.5)
Conjunctival hemorrhage	3 (1.4)	5 (2.4)
Instillation site pruritus	3 (1.4)	0
Eye discharge	1 (0.5)	3 (1.4)
Swelling of eyelid	1 (0.5)	4 (1.9)

AE, adverse event.

DISCUSSION

Efficacy Analysis

- In the ITTOD population, the mean improvement from baseline in ocular dryness and ocular discomfort scores was greater for reproxalap compared with vehicle at all timepoints from week 1 through week 12
- The least-squares (LS) mean difference (reproxalap – vehicle) for overall change from baseline in ocular dryness score from week 1 to week 12 was –8.5 (95% confidence interval [CI]: –12.6 to –4.5; *P*<.001)
- The LS mean difference (reproxalap – vehicle) for overall change from baseline in ocular discomfort score from week 1 to week 12 was –7.7 (95% CI: –11.8 to –3.5; *P*<.001)

Safety Analysis

- The most commonly reported AE was mild-to-moderate instillation site irritation
- Serious AEs were reported in 2 subjects in the reproxalap group and 3 subjects in the vehicle group; all serious AEs were nonocular and deemed unrelated to study treatment
- Slit-lamp biomicroscopy, visual acuity, IOP, and dilated funduscopy findings were unremarkable in both treatment groups