

Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease

Results of the Randomized Phase III OPUS-2 Study

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Purpose: Lifitegrast is an integrin antagonist that decreases T-cell-mediated inflammation associated with dry eye disease (DED). We report the results of OPUS-2, a phase III study evaluating the efficacy and safety of lifitegrast compared with placebo for the treatment of DED.

Design: A 12-week, multicenter, randomized, prospective, double-masked, placebo-controlled clinical trial.

Participants: Adults aged ≥ 18 years with use of artificial tears within 30 days, inferior corneal staining score ≥ 0.5 (0–4 scale), Schirmer tear test (without anesthesia) ≥ 1 and ≤ 10 mm, and eye dryness score ≥ 40 (0–100 visual analogue scale [VAS]).

Methods: Subjects were randomized 1:1 after 14-day placebo run-in to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 84 days.

Main Outcome Measures: Co-primary efficacy end points were change, from baseline to day 84, in eye dryness score (VAS, both eyes) and inferior corneal fluorescein staining score in the designated study eye. Secondary end points were change, from baseline to day 84, in ocular discomfort score (0–4 scale) in study eye, eye discomfort score (VAS), total corneal staining score in the study eye, and nasal conjunctival lissamine green staining score (0–4 scale) in the study eye. Treatment-emergent adverse events (TEAEs) were recorded.

Results: A total of 718 subjects were randomized: placebo, $n = 360$; lifitegrast, $n = 358$ (intent-to-treat population). Lifitegrast-treated subjects experienced greater improvement in eye dryness than placebo-treated subjects (treatment effect, 12.61; 95% confidence interval [CI], 8.51–16.70; $P < 0.0001$). There was no between-group difference in inferior corneal staining (treatment effect, 0.03; 95% CI, -0.10 to 0.17 ; $P = 0.6186$). There was nominally significant improvement of secondary symptom end points among lifitegrast-treated subjects: ocular discomfort (nominal $P = 0.0005$) and eye discomfort (nominal, $P < 0.0001$). There were no between-group differences on secondary signs: total corneal staining and nasal lissamine staining. More lifitegrast-treated subjects (33.7%) than placebo-treated subjects (16.4%) experienced ocular TEAEs; no ocular TEAEs were serious.

Conclusions: Lifitegrast met the co-primary symptom end point (eye dryness) but not the co-primary sign end point (inferior corneal staining). Secondary end point findings were consistent with this pattern. Most ocular TEAEs were mild to moderate; there were no unexpected TEAEs. Lifitegrast warrants further consideration as a treatment for DED. *Ophthalmology* 2015;122:2423–2431 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



*Supplemental material is available at www.aaojournal.org.

Dry eye disease (DED) is characterized by symptoms of eye dryness and discomfort and associated ocular surface inflammation.¹ Traditional treatment approaches in DED have typically included artificial tear substitutes, lubricant gels and ointments, nutritional supplements, topical cyclosporine, corticosteroids, and punctal plugs. However, many patients with DED continue to experience symptoms despite treatment.¹

Lifitegrast is a novel small-molecule integrin antagonist that blocks the interaction between intercellular adhesion molecule 1 and lymphocyte functional antigen 1, inhibiting T-cell adhesion, migration, activation, and subsequent

cytokine release and thereby decreasing T-cell-mediated inflammation known to be associated with DED.^{2–4} In a phase III study (OPUS-1), lifitegrast ophthalmic solution 5.0% administered twice daily for 84 days significantly reduced inferior corneal staining score, the prespecified co-primary end point, compared with placebo.⁵ However, there was no significant difference between groups in the co-primary symptom end point, change on the visual-related function subscale of a symptom scale.

No minimum visual-related subscale score was required for OPUS-1 eligibility, and baseline symptom severity was relatively mild.⁵ Evaluation of the OPUS-1 results led to

modifications in the design of OPUS-2, including removing the use of a controlled adverse environment (CAE)⁶ as a screening method, requiring a minimal threshold of disease severity at baseline on the symptom co-primary end point measure, and requiring recent use of artificial tears. In addition, on the basis of the reliability and sensitivity of the eye dryness score (visual analog scale [VAS]) measure in OPUS-1, eye dryness was chosen as the co-primary symptom end point in OPUS-2.

This report presents the results of the OPUS-2 study evaluating the efficacy and safety of lifitegrast ophthalmic solution 5.0% compared with placebo in the treatment of DED. Efficacy was assessed by the co-primary end points of change, from baseline to day 84, in eye dryness score and inferior corneal fluorescein staining score.

Methods

This was a 12-week, phase III, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel-arm study conducted in the United States (31 sites; 30 sites randomized subjects). The study was Health Insurance Portability and Accountability Act compliant and adhered to the tenets of the Declaration of Helsinki. Ethics committee approval was obtained before study initiation. All subjects provided written informed consent. The trial was registered at ClinicalTrials.gov (identifier NCT01743729).

Subjects

All study sites were community eye clinics in the United States. Study participants were identified through study sites' patient databases or through recruiting/advertising.

Eligible participants were adults (aged ≥ 18 years) who had self-reported history of DED, use of artificial tears within the past 30 days, best-corrected visual acuity of 0.7 logarithm of the minimum angle of resolution or better, corneal fluorescein staining score ≥ 2 (0–4 point scale) in ≥ 1 eye region, conjunctival redness score ≥ 1 (0–4 point scale) in ≥ 1 eye, eye dryness score ≥ 40 (0- to 100-point VAS) reported as a single score for both eyes, and positive response in ≥ 1 eye, defined as meeting the following criteria in the same eye at both visits 1 and 2: inferior corneal fluorescein staining score ≥ 0.5 and Schirmer tear test (without anesthesia) ≥ 1 and ≤ 10 mm. Subjects with secondary Sjögren's syndrome were eligible to participate if they were not taking systemic/ocular steroids, were not immunodeficient/immunosuppressed, and met all other inclusion and exclusion criteria.

The following individuals were excluded from participation in the study: women who were pregnant or might become pregnant;

those with contraindications or hypersensitivity to the investigational product, previous lifitegrast therapy, use of topical medications or antibiotics for treatment of blepharitis or meibomian gland disease, ocular herpes, ocular infection within the previous 30 days, blood donation or loss within the previous 56 days, ocular conditions or chronic illness that could affect study parameters, a disorder causing immunodeficiency, a history of LASIK or similar surgery within the previous 12 months, history of yttrium–aluminum–garnet laser posterior capsulotomy within the previous 6 months, or known history of alcohol or drug abuse that might interfere with study participation; those unwilling to discontinue wearing contact lenses during the study period; those using prohibited medications, including topical cyclosporine, any other ophthalmic medication, antihistamines, and aspirin during the prestudy washout period and study; and those with DED secondary to scarring or destruction of conjunctival goblet cells.

Study Protocol

The investigational product was supplied as a sterile solution containing 5.0% lifitegrast with ~ 0.2 ml in each unit dose vial. Trained study personnel administered the study drug and performed assessments. Ocular assessments such as staining procedures were performed by trained study physicians.

Subjects were randomly assigned to receive lifitegrast or placebo on the basis of a 1:1 ratio within the randomization strata using permuted blocks. Randomization was centralized across study centers and stratified by baseline inferior corneal fluorescein staining score in the study eye and baseline eye dryness score. An interactive Web response system was used to facilitate subject randomization.

During the screening period (days -14 to 0), subjects received twice-daily open-label placebo administered as a single eye drop in both eyes (Fig 1).

During the treatment period (days 0–84), subjects received twice-daily doses of lifitegrast ophthalmic solution 5.0% or placebo administered to the ocular surface as a single eye drop (in the morning and just before bedtime in the evening) in each eye. All study personnel were masked with regard to treatment assignments. Investigational product packaging was standardized such that lifitegrast and placebo were visually indistinguishable. No subjects were unmasked during the study.

Site staff administered the first dose of randomized investigational product on day 0 and a dose at each subsequent scheduled visit in the morning. Subjects self-administered the investigational product for all other doses. Treatment compliance was assessed by reconciliation of used and unused investigational product vials collected from subjects. Noncompliance was recorded as a protocol deviation if $>20\%$ of expected doses since the last visit were missed or $>120\%$ of expected doses were taken.

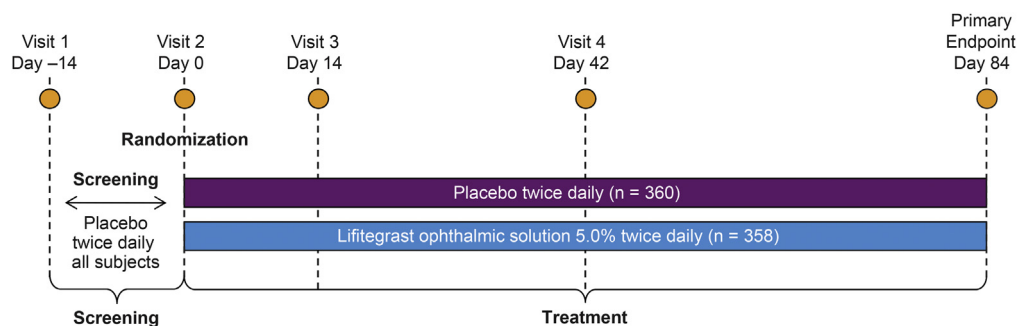


Figure 1. Study design.

During the washout and treatment periods, subjects were prohibited from using topical cyclosporine or any other ophthalmic medication, including artificial tears.

Outcome Measures

Efficacy parameters were assessed at each study visit (visit 1, day -14; visit 2, day 0; visit 3, day 14; visit 4, day 42; and visit 5, day 84). These included corneal fluorescein staining (0 = no staining, 4 = severe; 0.5-point increments; in the superior, central, and inferior corneal zones), conjunctival lissamine green staining (0 = no staining, 4 = severe; 0.5-point increments), VAS (a 7-item, subject-reported symptom index [0–100 scale; 0 = no discomfort, 100 = maximal discomfort] that includes items for eye dryness and eye discomfort), and ocular discomfort graded by the subject (0 = no discomfort, 4 = severe discomfort). For each subject, the eye with the worst (highest) inferior corneal fluorescein staining score at day -14 and day 0 was designated the study eye.

The co-primary efficacy end points were the eye dryness score (VAS, reported as a single score for both eyes) measured by mean change from baseline to day 84 and inferior corneal fluorescein staining score measured by mean change from baseline to day 84 in the designated study eye.

The secondary efficacy end points were change, from baseline to day 84, in ocular discomfort score in the designated study eye; eye discomfort score (VAS, reported as a single score for both eyes); total corneal staining score (derived sum of superior, central, and inferior corneal fluorescein staining scores; 0–12 points) in the designated study eye; and nasal conjunctival lissamine green staining score in the designated study eye.

Adverse events (AEs) recorded after the first randomized dose of investigational product were considered treatment-emergent adverse events (TEAEs). The investigators assessed adverse events for severity (mild, moderate, and severe).

Statistical Methods

Sample size was calculated as follows: for the primary ocular symptom, change in eye dryness score, a 10.0-unit difference between treatment groups in mean change from baseline to day 84 and a common standard deviation (SD) of 40 units were assumed on the basis of findings from the previous phase III trial.⁵ For the primary ocular sign, change in inferior corneal staining, a 0.25-unit difference, and a common SD of 0.95 units, were assumed, again on the basis of earlier study findings. Under both assumptions, a sample size of 350 per group would yield >90% power to show a significant difference at the $\alpha = 0.05$ level under a 2-sample *t* test.

The randomized population included all randomized subjects. The intent-to-treat (ITT) population and the safety population included all randomized subjects who received ≥ 1 dose of investigational product. The ITT population was the primary efficacy analysis population. Analyses conducted using the ITT population were based on treatment assigned, whereas analyses conducted using the safety population were based on treatment received.

For efficacy data, subjects were analyzed on observed data or last observation carried forward (LOCF). For analyses based on LOCF, data were taken from the last post-baseline date that data were collected.

For co-primary efficacy end points, each analysis was performed using a stratified 2-sample *t* test (using an analysis of variance [ANOVA] model) comparing lifitegrast with placebo in the ITT population with LOCF. The ANOVA model included treatment, strata, and the interaction between treatment and strata. The stratified 2-sample *t* test was done in PROC MIXED in SAS (SAS Institute Inc, Cary, NC) via the LSMEANS statement with the observed margins (OM) option and weights proportional to stratum sample

size. Statistical significance was required for both co-primary end points to test the secondary end points. Therefore, no adjustment for multiplicity was necessary for the co-primary end points.

Secondary efficacy end points were analyzed using the same ANOVA model as for the co-primary efficacy end points. Hochberg's procedure was applied to control the type I error rate at the 5% level across all secondary end points.

The incidence of ocular and nonocular TEAEs was tabulated by treatment group, system organ class, and preferred term (Medical Dictionary for Regulatory Activities version 14.1; MedDRA MSSO, McLean, VA).

The original study protocol was amended once on September 6, 2013. The study objectives and efficacy outcome measures were updated to clarify that they would be measured in the designated study eye, where appropriate, and be measured as the change from baseline to day 84 rather than as the day 84 score.

Results

Subject Disposition

A total of 1455 subjects were screened, representing 1450 unique subjects (Fig 2). Of the screened subjects, 557 did not enter the placebo run-in period because of screening failure, and a further 178 subjects were not randomized after the placebo run-in period because of screening failure.

The remaining 718 subjects were randomized, 360 to placebo and 358 to lifitegrast (ITT population). Data from each of these subjects were included in the efficacy analysis. A total of 49 subjects (12 in the placebo group and 37 in the lifitegrast group) discontinued treatment before day 84, so their data were analyzed via LOCF.

A total of 27 subjects, 13 in the placebo group and 14 in the lifitegrast group, were randomized but later found to not have met all inclusion/exclusion criteria, primarily because washout dates of previous medications could not be confirmed. All of these subjects were assessed by the sponsor and allowed to continue participation in the study, and they were included in the study analyses.

One subject was assigned to the placebo group but received lifitegrast via an incorrect kit at day 14 and was discontinued from the study. This subject was included in the lifitegrast group for the safety population, but in the placebo group for the randomized and ITT populations.

The first subject was randomized on December 20, 2012, and the last subject's last visit was on October 1, 2013.

Baseline Characteristics

Baseline characteristics were similar between treatment groups (Table 1). Subjects' ages ranged from 19 to 97 years, with a mean (SD) age of 58.8 (14.09) years. The majority of subjects were female, not Hispanic or Latino, and white. The most common iris colors were brown and blue.

The mean (SD) inferior corneal staining score at baseline was 2.40 (0.722) in the placebo group and 2.39 (0.763) in the lifitegrast group. The mean (SD) eye dryness score at baseline was 69.22 (16.761) in the placebo group and 69.68 (16.954) in the lifitegrast group. To promote balance of treatment assignment across baseline severity, randomization was stratified by inferior corneal fluorescein staining score (≤ 1.5 or > 1.5) and eye dryness score (< 60 or ≥ 60) in the study eye (Table 2). Most subjects (57.0%) had an inferior corneal fluorescein staining score > 1.5 and an eye dryness score ≥ 60 at randomization.

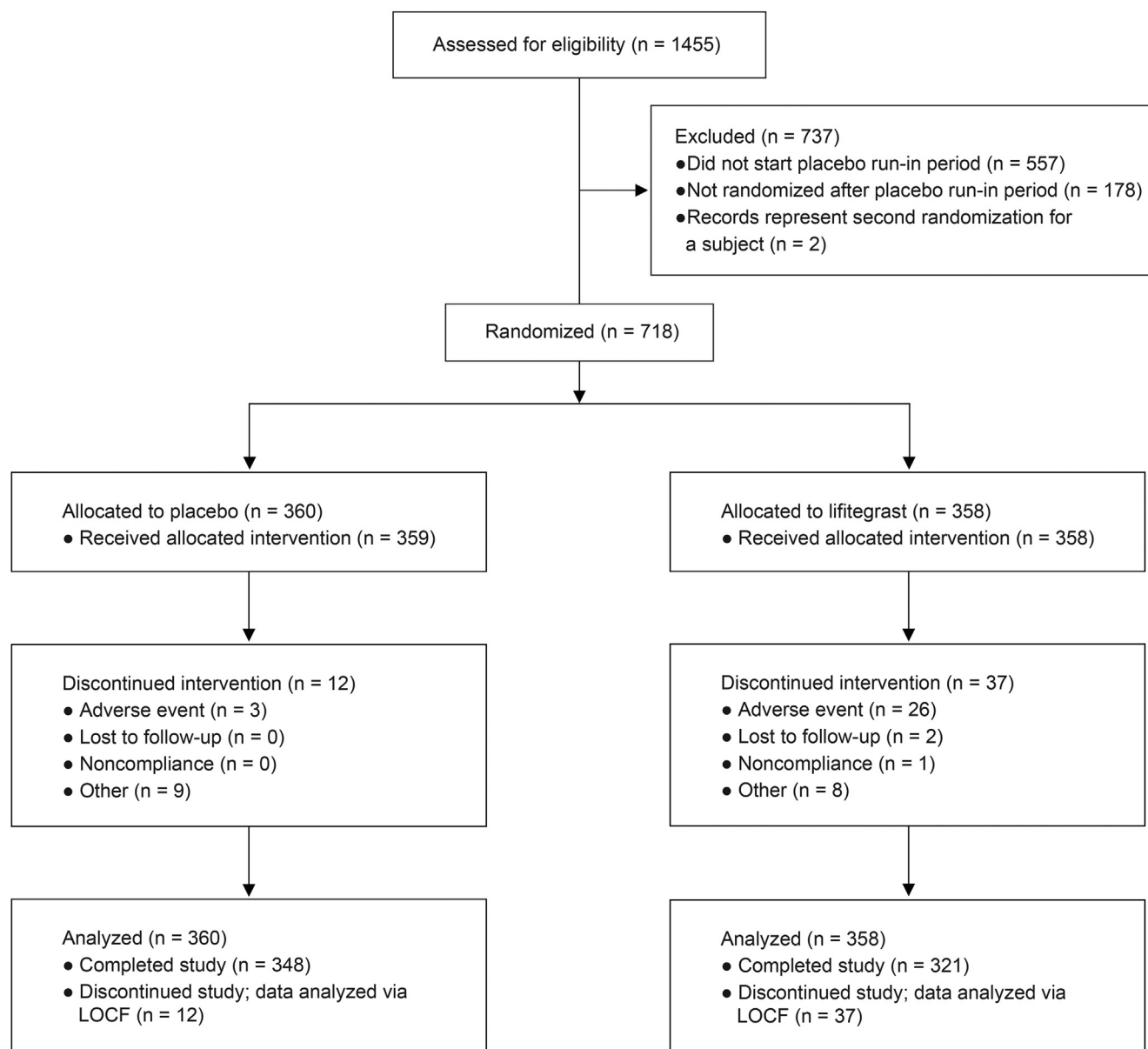


Figure 2. Participant flow. The total screening count of 1455 subjects includes 1450 unique subjects. One subject was assigned to the placebo group, but received lifitegrast via an incorrect kit at day 14 and was discontinued from the study. This subject was included in the lifitegrast group for the safety population (placebo, 359; lifitegrast, 359), but in the placebo group for the randomized and intent-to-treat populations (placebo, 360; lifitegrast, 358). LOCF = last observation carried forward.

All subjects had an ocular medical history of DED (the primary diagnosis). Other than the primary diagnosis, the most common (>10%) occurrences in ocular medical history were cataract (35.0%), cataract operation (14.9%), blepharitis (11.3%), and LASIK (10.9%). Within nonocular medical history, the most common (>10%) occurrences were hypertension (37.9%), postmenopause (29.4%), hysterectomy (19.8%), gastroesophageal reflux disease (17.3%), menopause (15.6%), hypothyroidism (15.5%), depression (14.5%), drug hypersensitivity (14.3%), hypercholesterolemia (12.0%), and hyperlipidemia (10.4%).

Overall, 5.2% of subjects took concomitant medications for ocular health, most commonly fish oil with minerals or vitamins (1.0% of subjects). Most (83.8%) subjects took concomitant non-ocular medications, most commonly acetylsalicylic acid, vitamins,

cholecalciferol, and fish oil. The proportions of subjects using particular concomitant medications were generally similar between treatment groups.

On the basis of investigational product vials returned, 95.5% of placebo-treated subjects and 93.0% of lifitegrast-treated subjects were compliant with study treatment.

Efficacy Findings

For the co-primary efficacy end point of eye dryness (VAS), the mean (SD) change from baseline to day 84 with LOCF was -22.75 (28.600) among placebo-treated subjects and -35.30 (28.400) among lifitegrast-treated subjects. The treatment effect was 12.61 (95% confidence interval [CI], 8.51–16.70; $P < 0.0001$) (Fig 3).

Table 1. Demographics of Randomized Population

Characteristic	Placebo (n = 360)	Lifitegrast (n = 358)	All Subjects (N = 718)
Age (yrs)			
Mean (SD)	58.9 (14.26)	58.7 (13.93)	58.8 (14.09)
≥75 yrs old, n (%)	42 (11.7)	39 (10.9)	81 (11.3)
Female sex, n (%)	265 (73.6)	285 (79.6)	550 (76.6)
Hispanic or Latino ethnicity, n (%)	64 (17.8)	79 (22.1)	143 (19.9)
Race, n (%)			
Asian	14 (3.9)	19 (5.3)	33 (4.6)
Black or African American	34 (9.4)	30 (8.4)	64 (8.9)
White	305 (84.7)	303 (84.6)	608 (84.7)
Other	7 (1.9)	6 (1.7)	13 (1.8)

SD = standard deviation.
Percentages are based on the number of subjects randomized.

For the co-primary efficacy end point of inferior corneal staining, placebo-treated subjects had mean (SD) change from baseline of -0.71 (0.943) compared with -0.73 (0.926) among lifitegrast-treated subjects. No between-group difference was observed (treatment effect, 0.03 ; 95% CI, -0.10 to 0.17 ; $P = 0.6186$).

A post hoc analysis based on the ITT population with observed data found that the treatment effect for eye dryness at day 14 was 6.67 (95% CI, 3.05 – 10.30 ; nominal $P = 0.0003$) and at day 42 was 10.63 (95% CI, 6.71 – 14.55 ; nominal $P < 0.0001$).

Per the statistical methodology of the study (described in the “Methods” section), statistical significance cannot be declared for the secondary end points because only 1 of the co-primary end point findings is statistically significant. Therefore, P values reported for hypothesis testing of secondary efficacy end points are referred to as nominal P values.

The mean (SD) change in ocular discomfort score from baseline to day 84 with LOCF was -0.57 (1.354) among placebo-treated subjects and -0.91 (1.280) among lifitegrast-treated subjects. The treatment effect was 0.34 (95% CI, 0.15 – 0.53 ; nominal $P = 0.0005$) (Fig 4).

For eye discomfort score (VAS), placebo-treated subjects had mean (SD) change from baseline of -16.73 (31.207) compared with -26.46 (31.238) among lifitegrast-treated subjects. The treatment effect was 9.77 (95% CI, 5.27 – 14.28 ; nominal $P < 0.0001$).

The mean (SD) change in total corneal fluorescein staining score from baseline to day 84 was -1.49 (2.097) among placebo-treated subjects and -1.62 (2.043) among lifitegrast-treated subjects. The treatment effect was 0.14 (95% CI, -0.16 to 0.44 ; nominal $P = 0.3711$).

For nasal lissamine staining score, placebo-treated subjects had mean (SD) change from baseline of -0.27 (0.805) compared

Table 2. Number of Subjects in Randomization Strata (Randomized Population)

Inferior Corneal Score at Baseline	Eye Dryness Score at Baseline	Placebo (n = 360), n (%)	Lifitegrast (n = 358), n (%)
≤1.5	<60	23 (6.4)	23 (6.4)
	≥60	29 (8.1)	31 (8.7)
>1.5	<60	99 (27.5)	100 (27.9)
	≥60	209 (58.1)	204 (57.0)

with -0.25 (0.850) among lifitegrast-treated subjects. The treatment effect was -0.02 (95% CI, -0.14 to 0.10 ; nominal $P = 0.6982$).

Safety Findings

The mean (SD) duration of treatment was similar between treatment groups (placebo, 82.1 [8.79] days; lifitegrast, 78.2 [17.87] days).

A higher percentage of subjects in the lifitegrast group experienced TEAEs and ocular TEAEs than in the placebo group (Table 3). The lifitegrast group had a higher frequency of subjects with ocular TEAEs considered possibly or probably related to the investigational product (11.1% and 17.3% , respectively) than the placebo group (7.8% and 2.5% , respectively).

A total of 29 subjects had TEAEs that led to treatment discontinuation; 26 of these were in the lifitegrast group. The most common ocular TEAEs that led to treatment discontinuation were instillation site irritation ($n = 5$), eye irritation ($n = 4$), and blepharitis ($n = 3$).

Seven subjects had serious TEAEs (placebo, $n = 4$; lifitegrast, $n = 3$), all of which were considered not related to the investigational product and resolved (except bladder cancer [placebo group] with an unknown outcome). No serious ocular TEAEs occurred during the study.

The most common TEAEs were reduced visual acuity, instillation site irritation (burning), instillation site reaction, and dysgeusia (change in taste sensation) (Table 4). Incidence of all recorded ocular TEAEs is reported in Table 5, and incidence of all nonocular TEAEs is reported in Table 6 (available at www.aaojournal.org).

Except for visual acuity reduced, all of these TEAEs were considered possibly or probably related to the investigation product by the investigator.

Most of the ocular and nonocular TEAEs in both treatment groups were mild to moderate in severity. Six subjects had ocular TEAEs considered severe, all in the lifitegrast group: instillation site irritation ($n = 2$), eye irritation ($n = 3$), and instillation site reaction ($n = 1$).

Overall, 41 subjects (placebo, $n = 23$; lifitegrast, $n = 18$) had an ocular TEAE of reduced visual acuity, 12 subjects (placebo, $n = 2$; lifitegrast, $n = 10$) had an ocular TEAE of blurred vision, and 1 subject (lifitegrast) had an ocular TEAE of visual impairment. All of these TEAEs were nonserious, and 4 of the TEAEs led to treatment discontinuation: visual acuity reduced ($n = 2$) and vision blurred ($n = 2$).

Discussion

Dry eye disease is a symptomatic disorder associated with chronic ocular surface inflammation. The OPUS-2 evaluated lifitegrast ophthalmic solution 5.0%, a novel investigational integrin antagonist, in improving the symptoms and signs of DED when administered topically twice daily for 12 weeks. The OPUS-2 demonstrated that lifitegrast-treated subjects experienced significantly greater improvement in subject-reported eye dryness compared with placebo-treated subjects. These findings were supported by similar outcomes for ocular discomfort and eye discomfort. To our knowledge, this is the first pivotal study to meet the prespecified symptom end points in a population with DED.

In a post hoc analysis of OPUS-2 data, the treatment benefit of lifitegrast over placebo for the symptom

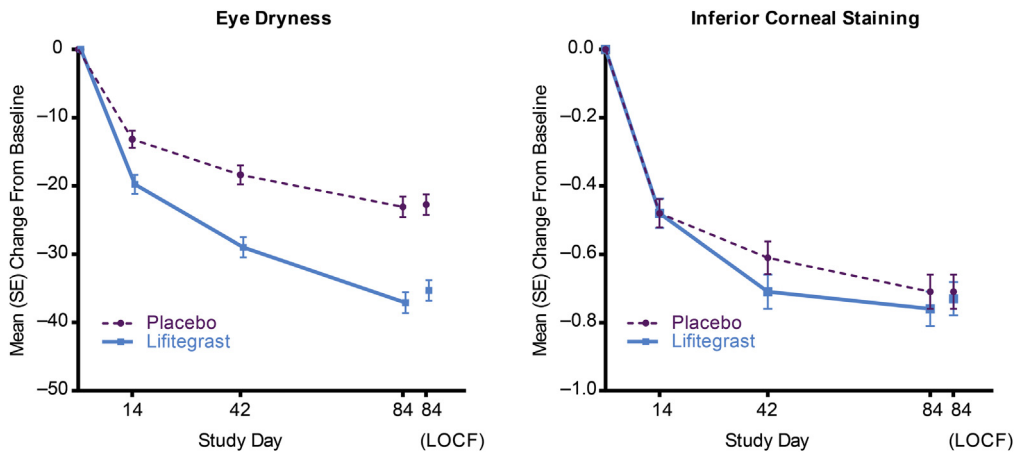


Figure 3. Co-primary efficacy end point results (intent-to-treat population). Graphs show observed data and end point with last observation carried forward (LOCF). SE = standard error.

co-primary efficacy end point, eye dryness score, was observed at day 14, the first post-treatment visit, and steadily increased until the last visit at day 84. A longer-term study is warranted to evaluate the potential for prolonged benefits beyond 12 weeks.

We believe the subjective outcomes in OPUS-2 are highly clinically relevant. On the basis of prior dry eye surveys conducted with the Dry Eye Questionnaire, dryness and discomfort tend to be the most consistent and worst symptoms reported by patients with DED; this served as the

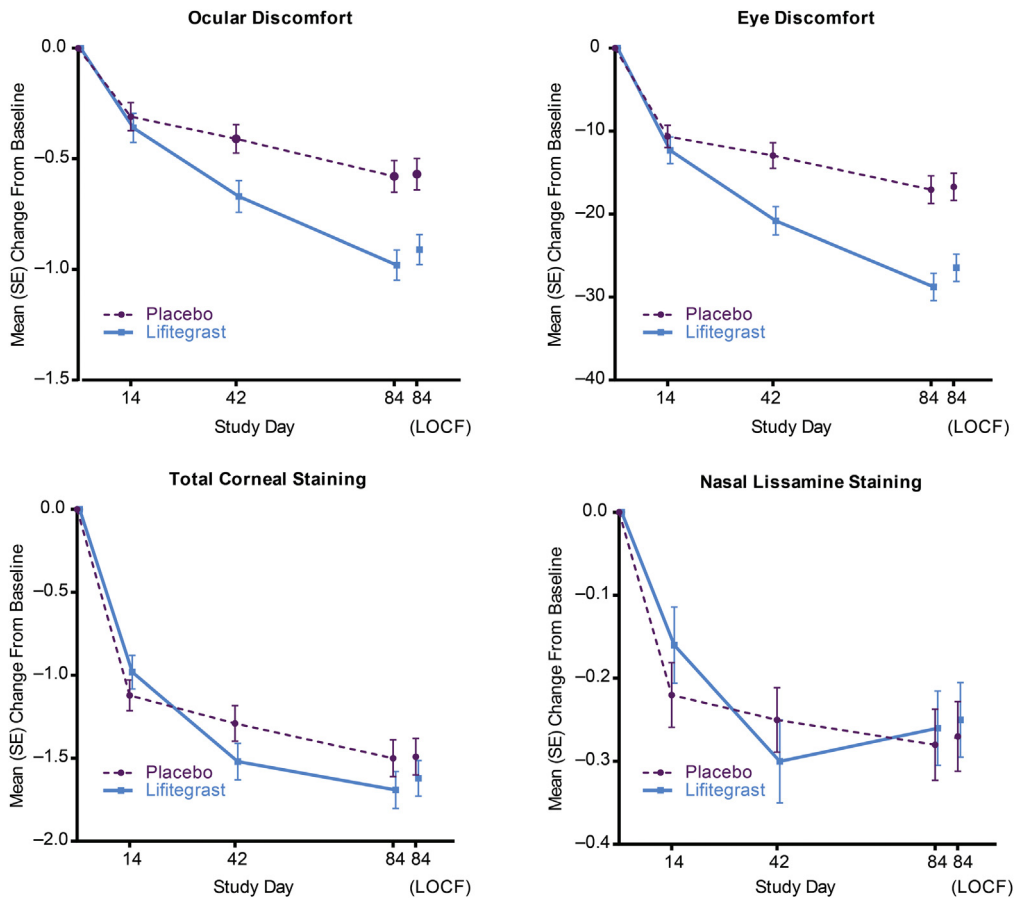


Figure 4. Secondary efficacy end point results (intent-to-treat population). Graphs show observed data and end point with last observation carried forward (LOCF). SE = standard error.

Table 3. Incidence of Treatment-Emergent Adverse Events (Safety Population)

	Placebo (n = 359), n (%)	Lifitegrast (n = 359), n (%)	All Subjects (N = 718), n (%)
Subjects with ≥1 ocular or nonocular TEAE	92 (25.6)	172 (47.9)	264 (36.8)
Ocular TEAEs	59 (16.4)	121 (33.7)	180 (25.1)
Mild	47 (13.1)	84 (23.4)	131 (18.2)
Moderate	12 (3.3)	31 (8.6)	43 (6.0)
Severe	0 (0)	6 (1.7)	6 (0.8)
Nonocular TEAEs	45 (12.5)	96 (26.7)	141 (19.6)
Mild	28 (7.8)	53 (14.8)	81 (11.3)
Moderate	14 (3.9)	35 (9.7)	49 (6.8)
Severe	3 (0.8)	8 (2.2)	11 (1.5)
Subjects with possibly or probably drug-related TEAEs	41 (11.4)	142 (39.6)	183 (25.5)
Ocular TEAEs	37 (10.3)	102 (28.4)	139 (19.4)
Mild	28 (7.8)	67 (18.7)	95 (13.2)
Moderate	9 (2.5)	30 (8.4)	39 (5.4)
Severe	0 (0)	5 (1.4)	5 (0.7)
Nonocular TEAEs	6 (1.7)	70 (19.5)	76 (10.6)
Mild	5 (1.4)	39 (10.9)	44 (6.1)
Moderate	1 (0.3)	28 (7.8)	29 (4.0)
Severe	0 (0)	3 (0.8)	3 (0.4)
Subjects prematurely withdrawn because of TEAEs	3 (0.8)	26 (7.2)	29 (4.0)
Ocular TEAEs	2 (0.6)	23 (6.4)	25 (3.5)
Nonocular TEAEs	1 (0.3)	6 (1.7)	7 (1.0)
Subjects with serious TEAEs	4 (1.1)	3 (0.8)	7 (1.0)
Ocular TEAEs	0 (0)	0 (0)	0 (0)
Nonocular TEAEs	4 (1.1)	3 (0.8)	7 (1.0)
Subjects with a TEAE resulting in death	0 (0)	0 (0)	0 (0)

Treatment-emergent adverse events (TEAEs) are defined as adverse events that occur after the start of randomized treatment; worst severity used if a subject had multiple adverse events in a group. Subjects were counted once per category per treatment. Medical Dictionary for Regulatory Activities version 14.1.

scientific rationale for the selection of the subjective end points in OPUS-2.^{7–10} Furthermore, the symptomatic treatment benefit observed with lifitegrast was replicated across 2 different psychometric instruments, the VAS (which measures holistic impressions in response to the prompted term) and the ocular discomfort score (which measures the symptom in the specific study eye), suggesting a consistent and broad response. Because subjects were prohibited from using any other ophthalmic medication, including artificial tears, during the course of the study, the significant improvement in symptoms can be attributed directly to treatment with lifitegrast.

Although OPUS-2 met its symptom co-primary end point, subjects treated with lifitegrast, compared with those receiving placebo, did not demonstrate significant

reductions in inferior corneal staining or conjunctival staining parameters, outcomes that were observed in the prior OPUS-1.⁵ In that study, lifitegrast-treated subjects had greater improvement in inferior corneal staining score than placebo-treated subjects ($P = 0.0007$).⁵ However, OPUS-1 did not meet the symptom co-primary end point. The disparity of the observed outcomes between the 2 studies is likely due to several factors, including but not limited to the multifactorial nature of DED, differences in experimental conditions and subject selection criteria, and, most important, the discordance of signs and symptoms in DED both in severity and in response to treatment.

The overall design of OPUS-2 was similar to that of OPUS-1⁵ with 3 main exceptions. First, in OPUS-1, subjects were screened using a CAE,⁶ whereas in OPUS-2, subjects

Table 4. Summary of Most Frequent (>5%) Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term	Placebo (n = 359), n (%)	Lifitegrast (n = 359), n (%)	All Subjects (N = 718), n (%)
Subjects with ≥1 ocular TEAE	59 (16.4)	121 (33.7)	180 (25.1)
Eye disorders	47 (13.1)	85 (23.7)	132 (18.4)
Reduced visual acuity	23 (6.4)	18 (5.0)	41 (5.7)
General disorders and administration site conditions	11 (3.1)	57 (15.9)	68 (9.5)
Instillation site irritation	5 (1.4)	28 (7.8)	33 (4.6)
Instillation site reaction	4 (1.1)	25 (7.0)	29 (4.0)
Subjects with ≥1 nonocular TEAE	45 (12.5)	96 (26.7)	141 (19.6)
Nervous system disorders	11 (3.1)	63 (17.5)	74 (10.3)
Dysgeusia	1 (0.3)	58 (16.2)	59 (8.2)

TEAE = treatment-emergent adverse event. Medical Dictionary for Regulatory Activities version 14.1.

were screened in the natural environment. Second, OPUS-1 did not require a minimum severity of the co-primary symptom end point for enrollment, whereas OPUS-2 required a minimum eye dryness score ≥ 40 at baseline. The combination of the use of CAE and no preset symptom threshold resulted in OPUS-1 enrolling subjects with dynamic ocular signs and mild to moderate symptoms. Third, in OPUS-2, subjects were required to have recent use of artificial tears, which increased the probability of enrolling subjects who were more symptomatic. As a result of these differences, OPUS-2 enrolled subjects with moderate to severe symptoms as assessed by baseline inferior corneal staining scores (OPUS-2, 2.40 points; OPUS-1, 1.83 points) and eye dryness scores (OPUS-2, 69.45 points; OPUS-1, 40.9 points),⁵ using a general definition of mild to moderate of < 2.0 points (4-point scale) for corneal staining and ≤ 40 points on the VAS (0–100 scale).

There may be a biological basis for the observed outcomes for the corneal staining end point in OPUS-2. For subjects with advanced corneal staining at baseline, there may be underlying corneal epithelial defects that increase the difficulty of demonstrating lifitegrast treatment response, whereas the drug response is readily observed in less-diseased corneas where there is sufficient capacity for epithelial repair and recovery in the presence of lifitegrast. In addition, the use of artificial tears, a requirement for enrollment in OPUS-2, may have reduced the prevalence of minor damages in corneal epithelium, making an effect during the study more difficult to detect.^{11,12}

The vast amount of data generated by the lifitegrast clinical studies provide further evidence that signs and symptoms function *independently* rather than *interdependently*.¹³ This lack of interdependency remains the core issue that has plagued DED researchers over the past 2 decades using co-primary end point study designs.

The safety profile of lifitegrast observed in OPUS-2 was similar to that in earlier clinical studies of lifitegrast.^{5,14} The most commonly reported TEAEs associated with lifitegrast were ocular instillation site symptoms (e.g., irritation) and dysgeusia (e.g., abnormal taste). Most ocular TEAEs were mild to moderate in severity, and there were no unexpected or unanticipated AEs. There were no reported ocular or drug-related serious TEAEs. There was no evidence of any localized ocular or systemic immunosuppressive complications. Overall, lifitegrast seemed to be well tolerated when administered twice daily for 12 weeks in this study.

Study Limitations

Limitations of OPUS-2 included selecting only subjects actively using artificial tears, limiting treatment duration to 12 weeks, and excluding subjects with known active lid margin disease. The rationale to limit subject selection to active artificial tear users was based on the assumption that subjects with significant DED symptomatology were more likely to be using artificial tears than subjects not actively using artificial tears. However, this is arguably an imprecise indicator of active DED because subjects may use artificial tears for reasons other than DED,^{15,16} and conversely, the study may have excluded subjects with advanced DED who

have given up using or never used artificial tears on a routine basis.¹⁵ Efficacy outcomes for lifitegrast beyond 12 weeks have not been evaluated. Given that DED is a chronic condition and may require long-term use of medication, additional long-term studies are necessary. Finally, the study population comprised primarily subjects with aqueous-deficient DED and specifically excluded subjects with active lid margin disease. Although many subjects with DED have mixed components of both lid margin disease and aqueous-deficient DED, the role of lifitegrast in managing the inflammatory component of predominately meibomian gland disease has not yet been evaluated.

In conclusion, OPUS-2 demonstrated that lifitegrast ophthalmic solution 5.0% significantly improved symptoms of eye dryness in subjects treated twice daily for 12 weeks compared with placebo. In combination with earlier studies showing that lifitegrast decreases corneal epitheliopathy,^{5,14} lifitegrast holds promise as a novel integrin antagonist for the treatment of both signs and symptoms of DED and warrants additional investigation.

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Footnotes and Financial Disclosures

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*A list of the members of the OPUS-2 investigators appears in the [Appendix](#) (available at www.aojournal.org).

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Abbreviations and Acronyms:

ANOVA = analysis of variance; **CAE** = controlled adverse environment; **CI** = confidence interval; **DED** = dry eye disease; **ITT** = intent-to-treat; **LOCF** = last observation carried forward; **SD** = standard deviation; **TEAE** = treatment-emergent adverse event; **VAS** = visual analogue scale.

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