

Lifitegrast for the Treatment of Dry Eye Disease

Results of a Phase III, Randomized, Double-Masked, Placebo-Controlled Trial (OPUS-3)

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Purpose: Lifitegrast is a lymphocyte function–associated antigen-1 antagonist developed to reduce inflammation in dry eye disease (DED). We report the results of OPUS-3 (NCT02284516), a phase III study evaluating the efficacy and safety of lifitegrast versus placebo in participants with DED.

Design: Twelve-week, phase III, randomized, double-masked, multicenter, placebo-controlled study.

Participants: Adults aged ≥ 18 years with Schirmer tear test (without anesthesia) ≥ 1 and ≤ 10 mm, corneal fluorescein staining score ≥ 2.0 (0–4 scale), eye dryness score (EDS) ≥ 40 (0–100 visual analogue scale [VAS]), and history of artificial tear use within 30 days of study entry.

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

Main Outcome Measures: The primary efficacy end point was change from baseline to day 84 in EDS. Key secondary efficacy end points were change from baseline to days 42 and 14 in EDS. Other secondary efficacy end points included additional VAS items (burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, pain), ocular discomfort score (ODS), and safety/tolerability of lifitegrast versus placebo.

Results: In the study, 711 participants were randomized: placebo, 356; lifitegrast, 355 (intention-to-treat [ITT] population). At day 84, lifitegrast-treated participants experienced significantly greater improvement from baseline in EDS versus those receiving placebo (treatment effect [TE], 7.16; 95% confidence interval [CI], 3.04–11.28; $P = 0.0007$). Mean changes from baseline in EDS also significantly favored lifitegrast on days 42 (TE, 9.32; 95% CI, 5.44–13.20; $P < 0.0001$) and 14 (TE, 7.85; 95% CI, 4.33–11.37; $P < 0.0001$). No statistically significant differences were observed in ODS between treatment groups at days 84, 42, or 14. A greater improvement was observed in lifitegrast-treated participants at day 42 in itching (nominal $P = 0.0318$), foreign body sensation (nominal $P = 0.0418$), and eye discomfort ($P = 0.0048$) versus participants receiving placebo. Most treatment-emergent adverse events were mild to moderate in severity; no serious ocular adverse events were reported.

Conclusions: Lifitegrast significantly improved symptoms of eye dryness, as measured by EDS, versus placebo in participants with DED. Improvement in EDS was observed as early as day 14. Lifitegrast appeared well tolerated. *Ophthalmology* 2017;124:53–60 © 2016 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/>).

Dry eye disease (DED) is a common ocular condition that can have a significant impact on daily functioning and quality of life.¹ Symptoms vary between patients and can include eye dryness, irritation, burning, foreign body sensation, and fluctuating visual disturbances. Although the cause of DED has not been fully elucidated, the available evidence suggests that inflammation of the ocular surface and lacrimal gland may have a key role in the pathogenesis of the disease and the downstream sequelae.²

Although some options are available to alleviate the signs or the symptoms of DED, such as artificial tear substitutes,

topical cyclosporine, topical or systemic corticosteroids, and punctal plugs,³ there remains a need for treatments that address both the symptoms and the resulting ocular surface damage. Lifitegrast ophthalmic solution 5.0% recently has been approved by the U.S. Food and Drug Administration for the treatment of signs and symptoms of DED in adult patients. Lifitegrast is a lymphocyte function–associated antigen-1 antagonist that blocks the binding of intercellular adhesion molecule-1 to lymphocyte function–associated antigen-1 on the T-cell surface, thereby inhibiting the T-cell recruitment, activation, and proinflammatory cytokine release associated with DED.⁴

Evidence supporting the efficacy and safety of treatment with lifitegrast ophthalmic solution 5.0% in DED is derived from the results of 4 previous randomized clinical trials. These included a phase II study,⁵ the phase III efficacy and safety trials OPUS-1⁶ and OPUS-2,⁷ and the 1-year safety trial SONATA.⁸ In all trials, lifitegrast appeared to be well tolerated. Review of results across the 3 trials that assessed efficacy reveals that lifitegrast improved DED signs (inferior corneal staining score [ICSS]) among participants with mild to moderate baseline symptomatology in the phase II study and OPUS-1, and DED symptoms (as measured by eye dryness score [EDS], visual analogue scale [VAS]) in participants with moderate to severe baseline symptomatology (EDS ≥ 40 and recent artificial tear use) in a post hoc analysis of OPUS-1, and as a co-primary end point in the OPUS-2 trial.^{5–7}

The objective of the OPUS-3 study was to evaluate the efficacy and safety of lifitegrast ophthalmic solution 5.0% compared with placebo in participants with DED of moderate to severe symptomatology to confirm the findings of symptom improvement demonstrated in OPUS-2.

Methods

This was a phase III, randomized, double-masked, multicenter, placebo-controlled study conducted in 41 study centers in the United States. The study was compliant with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki. Ethics committee approval was obtained before study initiation. All participants provided written informed consent. The trial was registered at ClinicalTrials.gov (identifier NCT02284516).

Participants

All participants were recruited from eye clinics in the United States. Patients were eligible if they were aged ≥ 18 years with a self-reported history of DED and all of the following: best-corrected visual acuity of ≥ 0.7 logarithm of the minimum angle of resolution in both eyes at visit 1, corneal fluorescein staining score ≥ 2 (0- to 4-point scale) in ≥ 1 region (superior, inferior, or central) in at least 1 eye, VAS score ≥ 40 for EDS in both eyes, conjunctival redness score ≥ 1 in at least 1 eye, use of artificial tears within 30 days before the screening visit, and a positive response in at least 1 eye specified as meeting the following criteria in the same eye at visits 1 and 2: ICSS ≥ 0.5 and Schirmer Tear Test (without anesthesia) ≥ 1 mm and ≤ 10 mm. Individuals with secondary Sjögren's syndrome were eligible to participate if they were not immunodeficient/immunosuppressed, were not taking systemic steroids, and met all other inclusion and exclusion criteria.

The following individuals were excluded from the study: women who were pregnant, men or women with hypersensitivity to the investigational product, previous randomization in a lifitegrast trial, use of any topical medication or antibiotic for the treatment of blepharitis or meibomian gland disease during the study, ocular herpes or any other ocular infection within 30 days of the screening visit, any blood donation or significant blood loss within 56 days of the screening visit, ocular conditions or chronic illness that could affect study parameters (e.g., glaucoma), a disorder causing immunodeficiency, history of LASIK or similar surgery within the previous 12 months, history of yttrium aluminum garnet-laser posterior capsulotomy in the past 6 months, known history of alcohol/drug abuse that might interfere with study participation,

those unwilling to avoid wearing contact lenses during the study period, and those with DED secondary to scarring or destruction of conjunctival goblet cells. Prohibited medications during the study were topical cyclosporine or any other ophthalmic medication, including artificial tears, antihistamines, corticosteroids, or mast cell stabilizers.

Study Protocol

The investigational product was supplied as a sterile, preservative-free, clear aqueous solution containing 5.0% lifitegrast with approximately 0.25 ml in each dose vial. During the screening period (days -14 to 0), all participants received twice-daily open-label placebo administered as a single eye drop in both eyes to assess compliance with twice-daily medication (Fig 1). During the treatment period (days $0-84$) (Fig 1), participants received twice-daily doses (upon awakening and just before bedtime) of lifitegrast ophthalmic solution 5.0% or matching placebo administered to the ocular surface as a single eye drop in each eye. Compliance with treatment was assessed by reviewing the returned investigational product from participants. Participants who were considered noncompliant (taking $<80\%$ or $>120\%$ of the expected doses between visits) after 2 consecutive visits were withdrawn from the study.

Participants were randomly assigned to treatment on the basis of a ratio of 1:1 (lifitegrast:placebo) within the randomization strata using permuted blocks. Randomization was centralized across study centers and stratified by baseline ICSS score (≤ 1.5 or >1.5) and EDS (<60 or ≥ 60) to ensure balance among the treatment groups. An interactive response technology was used to facilitate participant randomization accounting for the stratification factors. All study personnel were masked with regard to treatment assignments. Investigational product packaging was standardized such that lifitegrast and placebo were visually indistinguishable. The treatment assignment was not broken during the study.

Outcome Measures

The VAS and ocular discomfort score (ODS) were assessed at each study visit. The VAS is a 7-item, participant-reported symptom index (0–100 scale; 0 = no discomfort, 100 = maximal discomfort), with items of eye dryness, burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, and pain. Participants were asked to subjectively rate each ocular symptom (both eyes) by placing a vertical mark on the horizontal line of 0 to 100 to indicate the level of discomfort. The ODS was graded by the participant using a 5-point integer scale (0 = no discomfort, 4 = severe discomfort) for each eye at all study visits. The eye with the worst (highest) ICSS at day 0 was designated as the study eye.

The primary efficacy end point was change from baseline to day 84 in the EDS of the VAS. Key secondary efficacy end points were change from baseline to days 42 and 14 in EDS. The secondary efficacy end points were change from baseline to each visit in the 6 additional items of the 7-item VAS (burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, pain), change from baseline to each visit in the designated study eye in ODS, and safety and tolerability of lifitegrast compared with placebo. The VAS scores were reported as a single score for both eyes.

All adverse events (AEs) recorded after starting treatment with the investigational product were considered treatment-emergent AEs (TEAEs). The investigator assessed AEs for severity (mild, moderate, severe) and seriousness. Investigator verbatim terms were coded using the Medical Dictionary for Regulatory Activities (version 14.1) to Medical Dictionary for Regulatory Activities

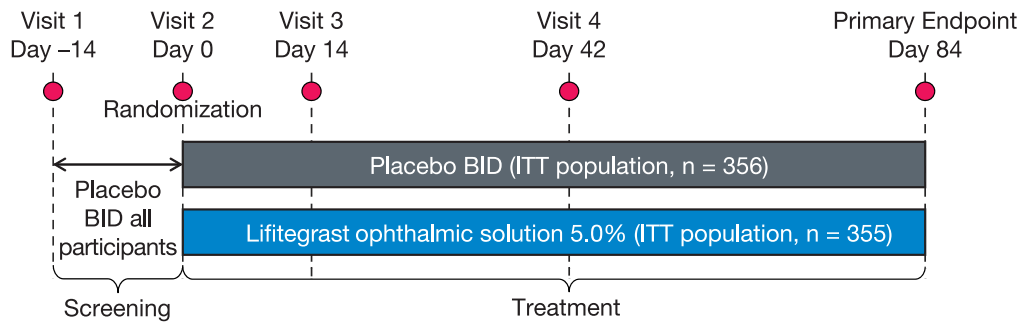


Figure 1. Study design. BID = twice daily; ITT = intention-to-treat.

Preferred Terms. By using this system, verbatim terms involving ocular burning on instillation of study drug were coded to the Preferred Term of instillation site irritation. Blurred/blurry vision, ocular discomfort, or drop discomfort on instillation (including drop comfort score [DCS] >3 at 15 minutes postinstillation) were coded to instillation site reaction. Verbatim terms for dysgeusia included but were not limited to bitter or metallic taste in the mouth on instillation.

Other safety assessments (measured at screening [visit 1], baseline [visit 2], and at subsequent visits for each eye) were conjunctival redness score (0 = none, 4 = severe; 0.5-point increments), corneal fluorescein staining score (0 = no staining, 4 = severe; 0.5-point increments), superior, central, and inferior corneal zones), conjunctival staining score with lissamine green (0 = no staining, 4 = severe; 0.5-point increments), Schirmer Tear Test, best-corrected visual acuity, slit-lamp biomicroscopy, and dilated fundoscopy. In addition, assessments of DCS (scale 0–10; 0 = very comfortable, 10 = very uncomfortable) were obtained at baseline and subsequent visits for each eye at instillation and at 1, 2, and 3 minutes after instillation. If the DCS was not ≤ 3 at 3 minutes the assessment was repeated at 5, 10, and 15 minutes until the DCS was ≤ 3 . If the DCS was >3 at 15 minutes, it was recorded as an AE (coded under instillation site reaction).

Statistical Methods

The overall type I error (2-sided 5% level) was maintained by sequential testing of hypotheses for the primary and 2 key secondary efficacy end points. A sample size of 350 participants per treatment group was estimated to ensure $>90\%$ power to detect a difference of 10.0 units (standard deviation [SD], 36.0) in the primary end point of mean change from baseline to day 84 in EDS between lifitegrast and placebo at a 2-sided 5.0% type I error, and $>85\%$ power to detect a difference of 8.0 units (SD, 34.0) in mean change from baseline to day 42 between the treatment groups, and $>80\%$ power to detect a difference of 6.5 units (SD, 30.0) in mean change from baseline to day 14 between treatment groups. The target treatment differences (and SDs) for the primary and key secondary efficacy end points were based on the results of the OPUS-2 study.⁷

All hypothesis tests were performed at the 2-sided 5% alpha level of significance, and associated 95% confidence intervals (CIs) were computed. Multiplicity adjustments were done for the primary and key secondary efficacy end points by sequential testing. The primary and key secondary end points were compared among the treatment groups using a stratified 2-sample *t* test (i.e., analysis of variance). The analysis of variance model included treatment, randomization strata, and the interaction between treatment and strata. This approach also was used to analyze the change from baseline to day 84 in ICSS.

The intention-to-treat (ITT) and safety populations included all randomized participants who received ≥ 1 dose of investigational product. All efficacy analyses were performed on the ITT population and presented by randomized treatment group. All safety analyses were performed on the safety population based on the treatment received. All efficacy analyses were performed using last observation carried forward, unless stated otherwise.

Protocol Amendments

The original study protocol was amended twice as follows: (1) On December 22, 2014, the exclusion criteria language was revised to specify prior randomization in a lifitegrast clinical study; and (2) on May 14, 2015, the schedule of assessments was updated to ensure the requirements for dilated fundoscopy were consistent throughout the protocol. The protocol also was revised to clarify that the investigators could use their discretion to determine whether DED progression or slit-lamp biomicroscopy changes that were considered not clinically significant should be considered as AEs.

Results

Participants

The study was conducted between November 2014 and October 2015. Of the 1542 participants screened, 711 participants were randomized (lifitegrast, $n = 355$; placebo, $n = 356$) (Fig 2) and 637 completed the trial. Two participants were randomized to the placebo group but erroneously received lifitegrast. These participants were included in the lifitegrast group for the safety population, but in the placebo group for the randomized and ITT populations.

Baseline characteristics were similar between treatment groups (Table 1). Participants' ages ranged from 18 to 93 years, with a mean (SD) age of 58.7 (14.47) years. The majority of participants were female (75.5%) and white (76.5%). All participants had an ocular medical history of DED (i.e., the primary diagnosis). Except for the primary diagnosis, the most common ($>10\%$) occurrences in ocular medical history for all participants were cataract (33.9%), cataract operation (13.1%), and keratomileusis (10.1%). In relation to nonocular medical history, the most common ($>10\%$) occurrences were hypertension (38.3%), postmenopause (35.3%), hysterectomy (20.7%), gastroesophageal reflux disease (18.6%), hypothyroidism (13.8%), drug hypersensitivity (12.5%), depression (12.2%), and hyperlipidemia (10.5%).

The mean (SD) ICSS score at baseline was 2.46 (0.744) in the placebo group and 2.46 (0.684) in the lifitegrast group; mean (SD) EDS was 69.0 (17.08) and 68.3 (16.88), respectively. The secondary efficacy end point of ODS at baseline corresponded to mild

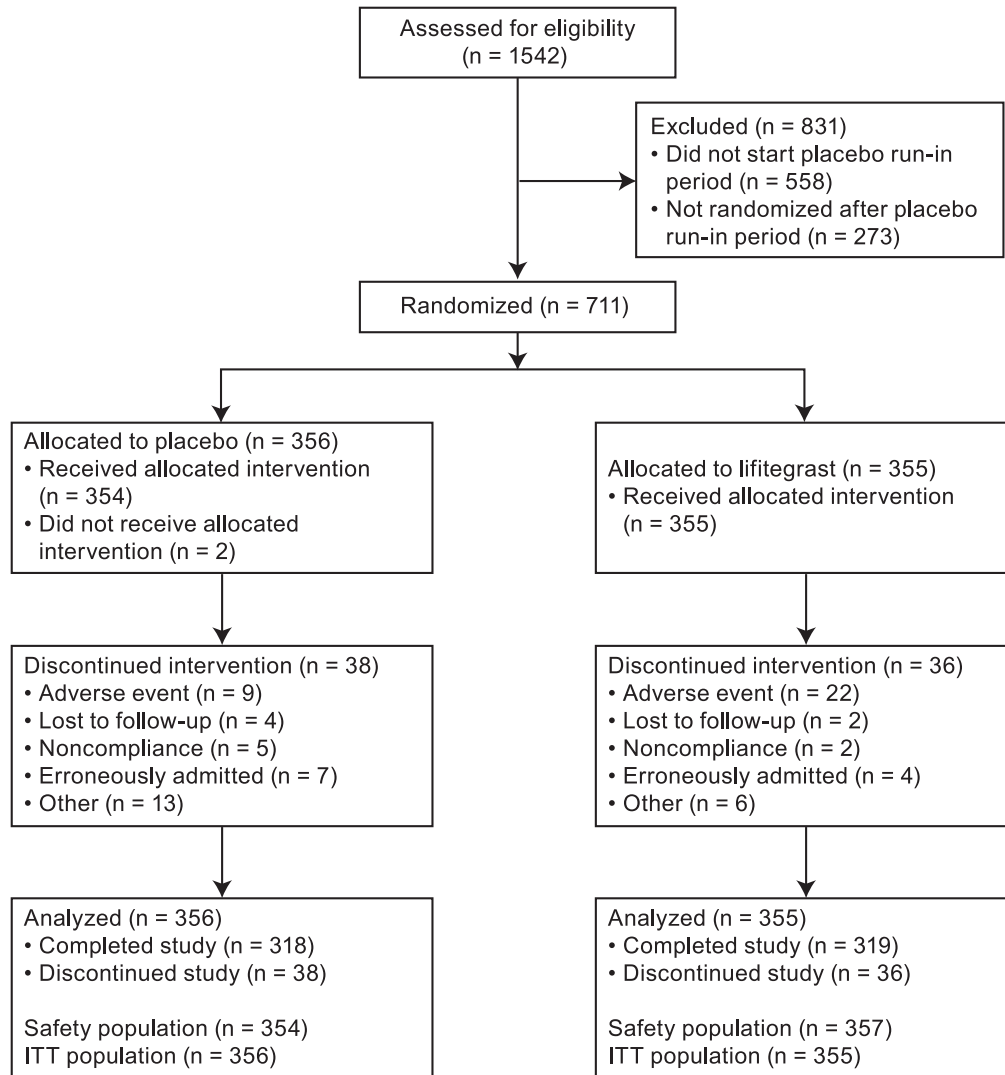


Figure 2. Participant flow. Two participants randomized to the placebo group erroneously received lifitegrast and thus were included in the lifitegrast group for the safety population and in the placebo group for the randomized and intention-to-treat (ITT) populations.

discomfort/awareness in both treatment groups (mean [SD] ODS: lifitegrast, 2.0 [1.14] vs. placebo, 2.0 [1.10]). To balance treatment assignment across baseline severity, randomization was stratified by ICSS (≤ 1.5 or > 1.5) and EDS (< 60 or ≥ 60) in the study eye (Table 2). Most participants (placebo, 54.8%; lifitegrast, 54.9%) had ICSS > 1.5 and EDS ≥ 60 at randomization.

Overall, 2.4% of participants took an ocular concomitant medication for ocular health with a start date on or after the first dose of investigational product. Although concomitant artificial tear use was not permitted per protocol, the most common ocular concomitant medication was Tears Plus (Allergan, USA; 0.4%). Overall, 78.9% of participants took concomitant nonocular medications. The most common ($> 10\%$) were acetylsalicylic acid (41.6%), Viterba (Pfizer, UK; vitamins; 13.4%), cholecalciferol (13.6%), and lisinopril (11.1%).

On the basis of investigational product vials returned, 97.6% of placebo-treated and 96.5% of lifitegrast-treated participants were compliant with study treatment. The mean (SD) duration of treatment was similar between treatment groups (placebo, 79.8 [17.37] days; lifitegrast, 79.3 [18.49] days).

Efficacy Findings

At day 84, lifitegrast-treated participants experienced significant improvement from baseline in EDS (VAS) versus participants receiving placebo (treatment effect [TE], 7.16; 95% CI, 3.04–11.28; $P = 0.0007$), meeting the primary efficacy end point (Fig 3). Mean changes from baseline in EDS (VAS) also significantly favored lifitegrast over placebo on day 42 (TE, 9.32; 95% CI, 5.44–13.20; $P < 0.0001$) and day 14 (TE, 7.85; 95% CI, 4.33–11.37; $P < 0.0001$), meeting both key secondary end points (Fig 3). The numbers of participants in each strata (ICSS [≤ 1.5 or > 1.5] and EDS [< 60 or ≥ 60]) were not high enough to allow meaningful conclusions regarding treatment response by strata.

Overall, ODS decreased during the study in both treatment groups, but there were no statistically significant differences in mean (standard error) change from baseline in ODS of the study eye between the groups at day 84 (TE, 0.04 [0.095]; $P = 0.6655$), day 42 (TE, 0.14 [0.090]; $P = 0.1293$), or day 14 (TE, 0.01 [0.089]; $P = 0.8893$).

Table 1. Demographics of Randomized Population

Characteristic	Placebo n = 356	Lifitegrast n = 355	Total n = 711
Age (yrs), mean (SD)	58.6 (14.84)	58.8 (14.10)	58.7 (14.47)
>65, no. (%)	137 (38.5)	128 (36.1)	265 (37.3)
>75, no. (%)	44 (12.4)	48 (13.5)	92 (12.9)
Female, no. (%)	269 (75.6)	268 (75.5)	537 (75.5)
Ethnicity, no. (%)			
Hispanic or Latino	58 (16.3)	60 (16.9)	118 (16.6)
Not Hispanic or Latino	298 (83.7)	295 (83.1)	593 (83.4)
Race, no. (%)			
American Indian or Alaskan Native	0	2 (0.6)	2 (0.3)
Asian	24 (6.7)	24 (6.8)	48 (6.8)
Black or African American	47 (13.2)	48 (13.5)	95 (13.4)
Native Hawaiian/other Pacific Islander	1 (0.3)	2 (0.6)	3 (0.4)
White	279 (78.4)	265 (74.6)	544 (76.5)
Other	5 (1.4)	14 (3.9)	19 (2.7)

SD = standard deviation.

Improvements from baseline were observed in both treatment groups for all VAS symptoms at days 84, 42, and 14, on the basis of last observation carried forward. Compared with the placebo group, a greater mean (standard error) improvement from baseline was observed in the lifitegrast group at day 42 for itching (TE, 4.17 [1.940]; nominal $P = 0.0318$), foreign body sensation (TE, 4.43 [2.172]; nominal $P = 0.0418$), and eye discomfort (TE, 5.86 [2.071]; nominal $P = 0.0048$). The mean changes from baseline to day 42 were similar between treatment groups for participant-reported burning/stinging, photophobia, and pain. The mean changes from baseline at days 14 and 84 were similar between treatment groups for all VAS symptoms except EDS.

Ad Hoc Analysis

An ad hoc analysis of ICSS in the ITT population demonstrated a reduction from baseline to day 84 that significantly favored lifitegrast over placebo (study eye; TE, 0.17; 95% CI, 0.03–0.30; nominal $P = 0.0144$). The 95% CI crossed zero on days 42 and day 14.

Safety Findings

Overall, a higher percentage of participants in the lifitegrast group (48.2%) had TEAEs than in the placebo group (24.6%) (Table 3). There also was a higher percentage of treatment-related TEAEs in the lifitegrast group (ocular, 35.3%; nonocular, 14.6%) than in the placebo group (ocular, 13.3%; nonocular, 0.8%).

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

Inferior Corneal Score at Baseline	Eye Dryness Score at Baseline	Placebo n = 356, No. (%)	Lifitegrast n = 355, No. (%)
≤1.5	<60	20 (5.6)	19 (5.4)
	≥60	33 (9.3)	32 (9.0)
>1.5	<60	108 (30.3)	109 (30.7)
	≥60	195 (54.8)	195 (54.9)

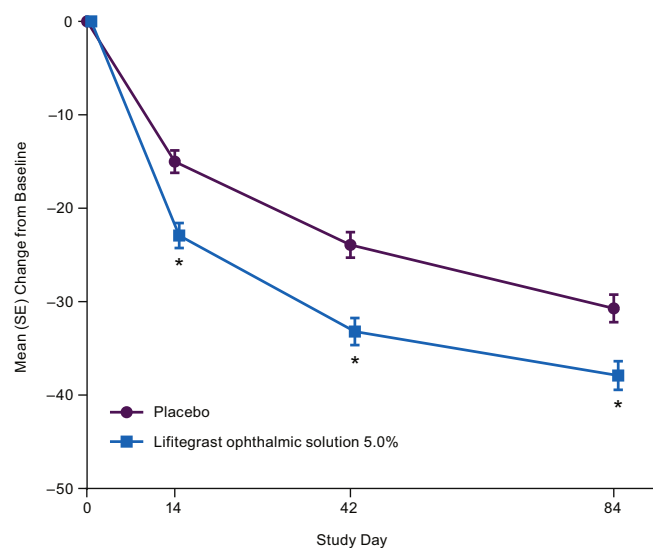


Figure 3. Eye dryness score (EDS) (visual analogue scale [VAS]); intention-to-treat population with last observation carried forward. EDS (0- to 100-point VAS; both eyes). Treatment effect, * $P = 0.0007$ (day 84), $P < 0.0001$ (days 42 and 14). SE = standard error.

Most ocular and nonocular TEAEs were mild to moderate in severity, and few participants had severe ocular (0.6%) or nonocular (1.0%) TEAEs. Eight serious TEAEs were reported (placebo, 1.1%; lifitegrast, 1.1%), all of which were nonocular and considered not related to the study drug by the investigator. No serious ocular TEAEs were reported (Table 3).

The most common ocular TEAEs, occurring in >5% of participants in either treatment group, were instillation site irritation and instillation site reaction, all cases of which were mild to moderate in severity. The most common nonocular TEAE was dysgeusia (placebo, $n = 1$ [0.3%]; lifitegrast, $n = 46$ [12.9%]) (Table 3), which was also mild to moderate in all affected participants. No other nonocular TEAE was reported by >5 participants. Similar proportions of participants in each treatment group reported nonocular infections and infestations (lifitegrast, 3.4%; placebo, 3.1%), and the observed safety profile demonstrated no pattern of AEs suggesting systemic toxicities, localized or systemic infections, or immunosuppressive complications.

Discontinuations due to TEAEs were infrequent (lifitegrast, 5.9%; placebo, 2.5%) (Table 3). The most common TEAEs that led to treatment discontinuation were instillation site reaction (placebo, $n = 2$; lifitegrast, $n = 5$) and instillation site irritation (placebo, $n = 0$; lifitegrast, $n = 4$). A total of 9 participants were discontinued from treatment because of a nonocular TEAE (placebo, $n = 3$; lifitegrast, $n = 6$). Each nonocular TEAE that led to treatment discontinuation occurred in only 1 participant, with the exception of headache that occurred in 2 participants in the lifitegrast group. In both treatment groups, most ocular and nonocular TEAEs that led to discontinuation were considered mild to moderate in severity and resolved.

Other Ocular Safety Parameters

Although the magnitude of change was small, conjunctival redness score, corneal fluorescein staining score (including ICSS, ad hoc analysis reported earlier), conjunctival lissamine green staining, and Schirmer tear test displayed greater numeric improvement over

Table 3. Summary of Ocular and Nonocular Treatment-Emergent Adverse Events (Safety Population)

TEAEs, no. (%)	Placebo n = 354	Lifitegrast n = 357	Total n = 711
Participants with ≥ 1 TEAE	87 (24.6)	172 (48.2)	259 (36.4)
Ocular TEAEs	63 (17.8)	141 (39.5)	204 (28.7)
Mild	46 (13.0)	113 (31.7)	159 (22.4)
Moderate	15 (4.2)	26 (7.3)	41 (5.8)
Severe	2 (0.6)	2 (0.6)	4 (0.6)
Nonocular TEAEs	29 (8.2)	84 (23.5)	113 (15.9)
Mild	20 (5.6)	60 (16.8)	80 (11.3)
Moderate	8 (2.3)	18 (5.0)	26 (3.7)
Severe	1 (0.3)	6 (1.7)	7 (1.0)
Participants with TEAEs considered possibly or probably drug related	50 (14.1)	136 (38.1)	186 (26.2)
Ocular TEAEs	47 (13.3)	126 (35.3)	173 (24.3)
Nonocular TEAEs	3 (0.8)	52 (14.6)	55 (7.7)
Participants prematurely withdrawn due to ≥ 1 TEAE	9 (2.5)	21 (5.9)	30 (4.2)
Ocular TEAEs	6 (1.7)	17 (4.8)	23 (3.2)
Nonocular TEAEs	3 (0.8)	6 (1.7)	9 (1.3)
Participants with serious TEAEs	4 (1.1)	4 (1.1)	8 (1.1)
Ocular TEAEs	0	0	0
Nonocular TEAEs	4 (1.1)	4 (1.1)	8 (1.1)
Summary of most frequent ($>5\%$) TEAEs			
Instillation site irritation*	11 (3.1)	65 (18.2)	76 (10.7)
Instillation site reaction*	19 (5.4)	45 (12.6)	64 (9.0)
Dysgeusia*	1 (0.3)	46 (12.9)	47 (6.6)

TEAE = treatment-emergent adverse event.

*Verbatim terms coding to instillation site irritation, instillation site reaction, and dysgeusia are given in the "Methods" section.

time in the lifitegrast group compared with that in the placebo group.

In the lifitegrast group, numeric improvements in mean DCS of the study eye at instillation were observed across visits (baseline to day 84). On days 14, 42, and 84, the majority (64%–66%) of participants reported DCS <3 at 3 minutes postinstillation. For participants with DCS >3 at 3 minutes, the mean DCS in the lifitegrast group was similar to or better than that in the placebo group at 5, 10, and 15 minutes.

Discussion

In this study, lifitegrast met the primary end point of change from baseline in patient-reported symptoms, as measured by EDS in participants with DED with moderate to severe baseline symptomatology and a history of recent artificial tear use. The therapeutic benefit of lifitegrast on EDS was observed as early as 2 weeks. Lifitegrast was generally well tolerated, and the safety profile was consistent with previous lifitegrast trials. OPUS-3 replicated, and therefore confirmed, the results from the OPUS-2 study in a comparable study population. This finding is noteworthy because, according to our knowledge, statistically significant symptom improvements have not been demonstrated before in 2 separate phase III clinical studies of an investigational drug therapy for DED.

The data from this study add to the clinical evidence accumulated from the lifitegrast trials to date, which comprise >2500 patients. In terms of safety, all 5 lifitegrast studies, including the 1-year safety study SONATA, demonstrated that lifitegrast was generally well tolerated, with no serious ocular TEAEs. Overall, the efficacy results

from OPUS-2 and OPUS-3 suggest that lifitegrast improves symptoms of DED in participants with moderate to severe baseline symptomatology. A post hoc analysis of OPUS-1 also showed symptom improvement among participants with this severity of baseline symptomatology. Significant improvements versus placebo in EDS were observed at days 84, 42 and 14 in OPUS-3. Of particular note, the observation that lifitegrast significantly improved EDS compared with placebo as early as day 14 is consistent with findings from OPUS-2; this early effect of treatment could represent an appreciable benefit in treating patients with DED. A numeric improvement from baseline in EDS also was observed over time in the placebo group, which may have reduced TE. Such a placebo effect is not uncommon in DED trials in which patient-reported outcome measures are used,⁹ but we believe it does not diminish the robustness of the primary outcome.

In contrast to the effect on symptoms, in prior studies, improvements in signs with lifitegrast have appeared to be most marked among those with mild to moderate baseline symptomatology. Because of this discordance between sign and symptom results in prior studies, the OPUS-3 trial was designed to specifically evaluate symptom effects in the population with moderate to severe DED, and signs were included as part of the safety assessment. Positive trends were observed in OPUS-3 for conjunctival redness score, corneal fluorescein staining score, conjunctival lissamine green staining, and Schirmer tear test with lifitegrast versus the placebo group.

Among the secondary symptom end points, significant differences between lifitegrast and placebo were observed for change from baseline to day 14 in VAS items of

itching, foreign body sensation, and eye discomfort. However, other secondary end points, including ODS and VAS items of burning/stinging, photophobia, and pain, did not show significant differences between treatment groups at any time point measured. This finding may relate to how patients describe their DED symptoms. For example, patients can use different words to describe the same symptom, reflecting individual preferences or influence during the clinical study (learned word choice).¹⁰ The EDS may be the best to capture patient response to treatment, as suggested by a number of clinical studies in which dryness was the most frequently reported symptom.^{11–14}

Overall in this study, lifitegrast was well tolerated, with no serious ocular TEAEs reported; <5% of patients in the lifitegrast group discontinued because of ocular TEAEs. The most common ocular TEAEs considered related to lifitegrast were instillation site irritation and instillation site reaction, which were mild to moderate in severity and occurred in 18.2% and 12.6% of lifitegrast-treated participants, respectively. These AEs led to discontinuations in only a small proportion of participants (1.1% and 1.4% of the lifitegrast treatment group, respectively). In addition to safety, the comfort of an ophthalmic formulation when instilled in the eye is an important consideration when evaluating the suitability of a drug therapy for DED, because it may affect patient adherence to the treatment. We found that drop tolerability after instillation was acceptable and improved within 3 minutes of instillation, reaching values close to those in the placebo group. Consistent reductions in DCS also occurred across visits suggesting that drop tolerability of lifitegrast improves with time, which is consistent with observations in prior trials.^{6–8}

The proportion of lifitegrast-treated participants with nonocular TEAEs appeared high in this study (lifitegrast, 23.5% vs. placebo, 8.2%). However, as with ocular TEAEs, most nonocular TEAEs were mild to moderate in severity. The most common nonocular TEAE was dysgeusia, which occurred in 12.9% of participants in the lifitegrast group compared with 0.3% of participants in the placebo group, and was mild to moderate in severity in all affected participants. Dysgeusia is a relatively common AE associated with instillation of some topical ophthalmic medications and led to discontinuation of treatment in just 1 participant in the lifitegrast group. Other than dysgeusia, no individual nonocular TEAEs occurred in more than 5 participants. The pattern of AEs in this study did not suggest any evidence of systemic toxicities, infections, or immunosuppressive complications.

Study Limitations

Limitations of this study were the relatively short treatment period of 84 days and a study population that was limited to patients with at least moderate baseline symptomology. Other limitations were that patients with a history of LASIK within 12 months before the study and those wearing contact lenses were excluded from this study, so the efficacy and safety of lifitegrast in these groups were not studied. In

addition, the study was not powered or designed to assess corneal staining or other exploratory variables.

In conclusion, building on the cumulative evidence from prior lifitegrast trials, this study demonstrates that lifitegrast significantly improved patient-reported symptoms of DED, as measured by the EDS, from as early as 2 weeks. Lifitegrast was generally well tolerated, and there were no serious ocular TEAEs. On the basis of the results from OPUS-3 and previous trials, lifitegrast seems to be a promising lymphocyte function–associated antigen-1 antagonist therapy for the treatment of signs and symptoms of DED.

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Abbreviations and Acronyms:

AE = adverse event; **CI** = confidence interval; **DCS** = drop comfort score; **DED** = dry eye disease; **EDS** = eye dryness score; **ICSS** = inferior corneal staining score; **ITT** = intention-to-treat; **ODS** = ocular discomfort score; **SD** = standard deviation; **TE** = treatment effect; **TEAE** = treatment-emergent adverse event; **VAS** = visual analogue scale.

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