FAX

Company: Shire

TO:

Name: John McCall, R.Ph.

Fax Number: (888) 656-6822

Date: 10/31/2016 # of Pages: 21
(including cover sheet)

FROM:

Name: Mauricio Munoz, Pharm.D.

Contact Number: (714) 316-3249

Subject: AK P&T Committee: Pre-Review Submission ☐ Urgent ☐ Please Reply

Message:

Dr. McCall,

Please see the following Submission Request Form for Pharmaceutical Manufacturers as well as copies of the published citations. Full pdf copies for each of the articles are also freely available on the following websites:

OPUS 2: http://www.aaojournal.org/article/S0161-6420(15)00777-0/abstract

Mechanism of action: http://www.theocularsurfacejournal.com/article/S1542-0124(16)00010-0/abstract

Please let me know if any additional information is needed. I will be attending the Alaska Medicaid P&T Committee meeting.

Kind regards,
Mauricio Munoz, Pharm.D.
Sr. Medical Science Liaison
Shire
Mobile: (714) 316-3249
E-mail: mamunoz@shire.com

Print Form Reset Form

State of Alaska Department of Health and Social Services, Division of Health Care Services

Submission Request Form for Pharmaceutical Manufacturers

Fax this request to: 1-888-656-6822 ATTN: John McCall, R.Ph.

Note: Processing May be Delayed if Information Submitted is Illegible or Incomplete

Members of the Pharmacy and Therapeutics (P&T) Committee have requested that all clinical information, questions, or comments about the Preferred Drug List (PDL) be sent directly to Magellan Medicaid Administration. Manufacturers and other interested parties have been requested not to contact the members directly. Written comments on the PDL from all interested parties should be submitted to Erin Narus, PharmD, R.Ph. at the State of Alaska.

Note: Manufacturers submitting comments are requested to do so through their Product Manager using this form. This form constitutes a request for *NEW* information pertaining to peer-reviewed literature including off-label peer-reviewed studies.

Contact Information

MANUFACTURER NAME: Shire Pharmaceuticals

DATE: 10 - 31 - 2016

PRODUCT MANAGER'S NAME: Mauricio Munoz, Pharm.D.

TITLE: Sr. Medical Science Liaison

ADDRESS: 6931 Rio Vista Drive

CITY: Huntington Beach

STATE: CA

ZIP CODE: 92647

PHONE NUMBER: 714 - 316 - 3249

FAX NUMBER: - -

PRODUCT: Xiidra (lifitegrast ophthalmic solution) 5%

Clinical Rationale Request for Consideration (If additional space is required, use Clinical Rationale Continuation Page).

The U.S. Food and Drug Administration approved Xiidra (lifitegrast ophthalmic solution) for the treatment of signs and symptoms of dry eye disease, on Monday, July 11, 2016. Xiidra is the first medication in a new class of drugs, called lymphocyte function-associated antigen 1 (LFA-1) antagonist, approved by the FDA for dry eye disease.

Magellan HEALTH℠

State of Alaska Department of Health and Social Services, Division of Health Care Services
Submission Request Form for Pharmaceutical Manufacturers

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Published Citations (If additional space is required, use Published Citations Continuation Page).

Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study.
Sheppard JD, Torkildsen GL, Lonsdale JD, D'Ambrosio FA Jr, McLaurin EB, Eiferman RA, Kennedy KS, Semba CP; OPUS-1 Study Group.
Ophthalmology. 2014 Feb;121(2):475-83. PMID: 24289915

Lifitegrast, a Novel Integrin Antagonist for Treatment of Dry Eye Disease.
Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Haque R.
Ocul Surf. 2016 Apr;14(2):207-15. PMID: 26807723

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AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

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

Results of the Randomized Phase III OPUS-2 Study

*Joseph Tauber, MD,[1] Paul Karpecki, OD,[2] Robert Latkany, MD,[3] Jodi Luchs, MD,[4] Joseph Martel, MD,[5] Kenneth Sall, MD,[6] Aparna Raychaudhuri, PhD,[7] Valerie Smith, MBA,[7] Charles P. Semba, MD,[7] for the OPUS-2 Investigators**

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

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ISSN 0161-6420/15

modifications in the design of OPUS-2, including removing the use of a controlled adverse environment (CAE)[5] 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.

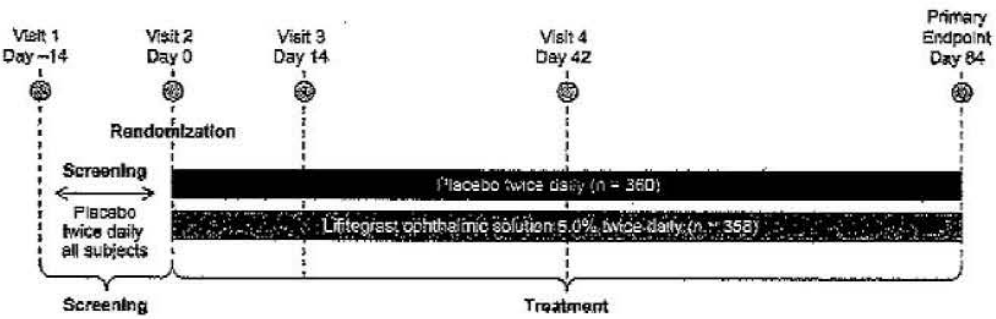

Figure 1. Study design.

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.

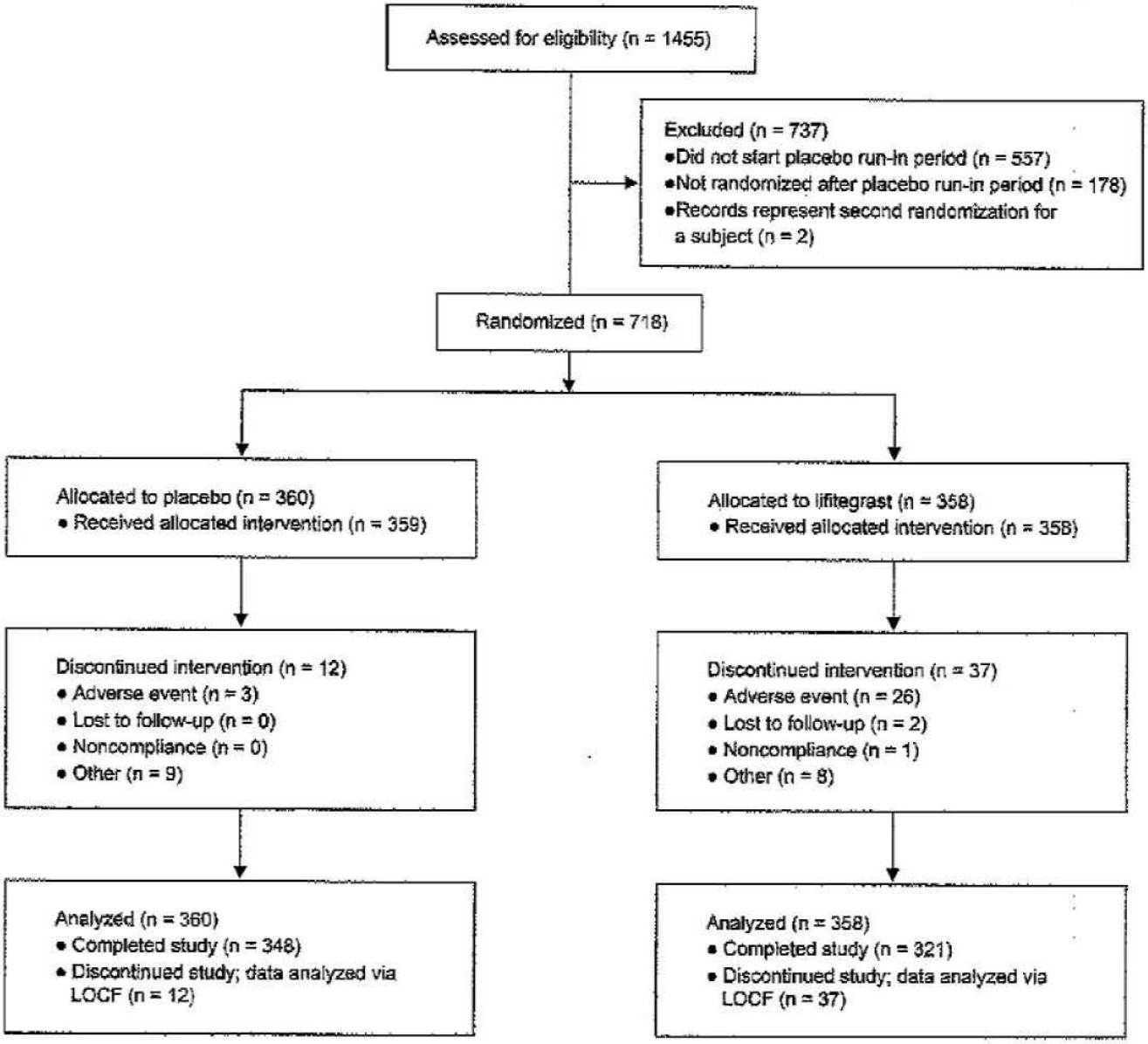

Figure 2. Participant flow. The total screening count of 1455 subjects includes 1450 unique subjects. One subject was assigned to the placebo group, but received lifitegrast via an incorrect kit at day 14 and was discontinued from the study. This subject was included in the lifitegrast group for the 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 nonocular 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 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).

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)

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

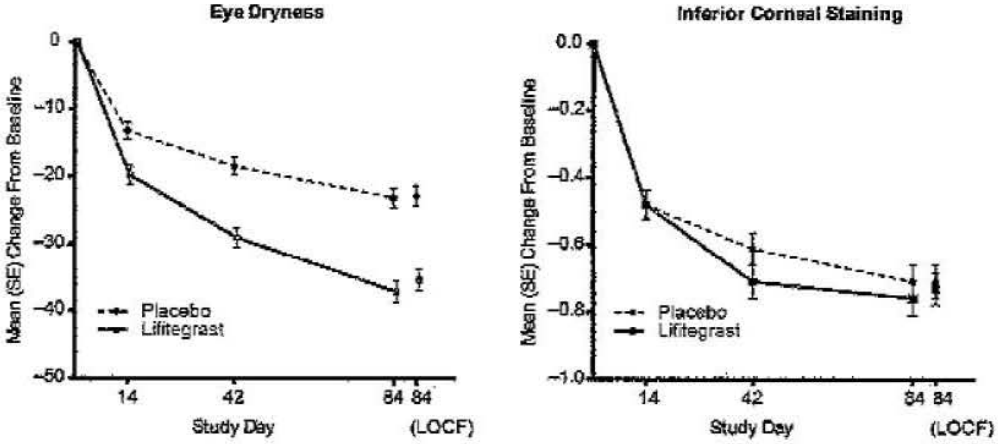

Figure 3. Co-primary efficacy end point results (intent-to-treat population). Graphs show observed data and end point with last observation carried forward (LOCF). SE = standard error.

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

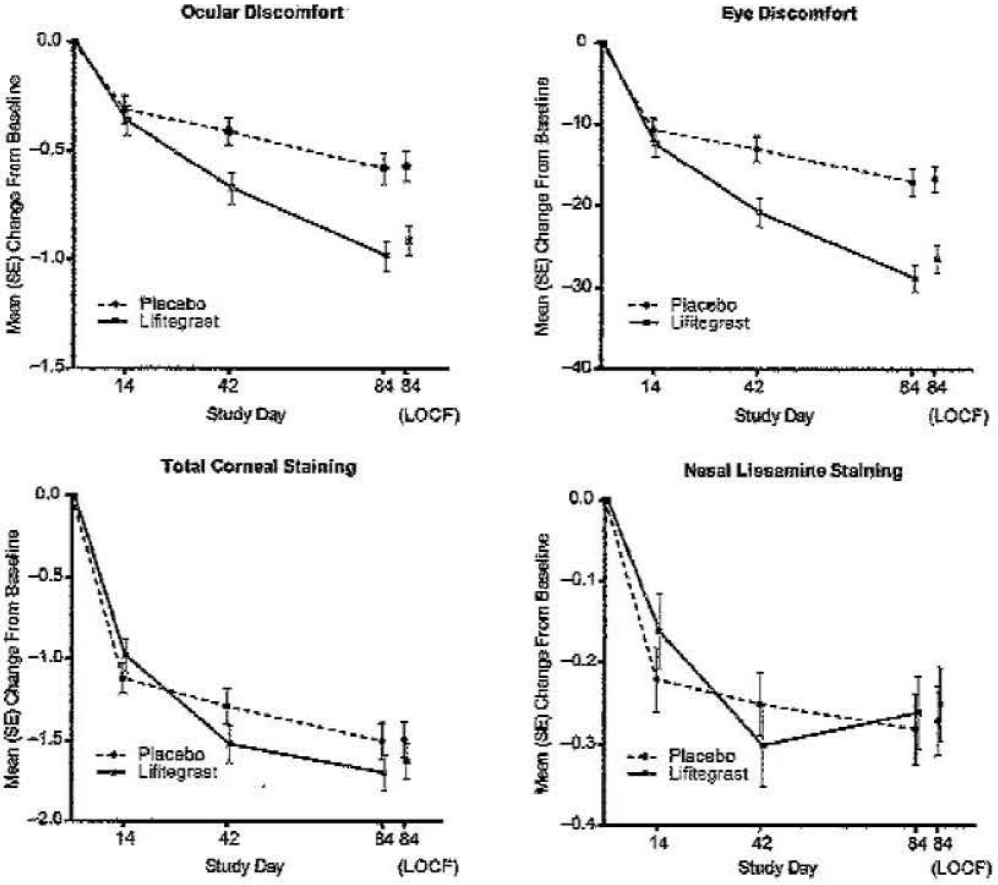

Figure 4. Secondary efficacy end point results (intent-to-treat population). Graphs show observed data and end point with last observation carried forward (LOCF). SE = standard error.

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-1[5] 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.[13] 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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*A list of the members of the OPUS-2 investigators appears in the Appendix (available at www.aaojournal.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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Innovative Techniques and Technology

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Lifitegrast, a Novel Integrin Antagonist for Treatment of Dry Eye Disease

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ABSTRACT The etiology of dry eye disease (DED) is complex and not yet fully understood, but the disease is now recognized as being associated with ocular surface inflammation. The latest advances in the understanding of the pathophysiology of DED have directed the focus of recent drug development to target the inflammatory pathways involved in the disease. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of two important cell surface proteins (lymphocyte function-associated antigen 1 and intercellular adhesion molecule 1), thus lessening overall inflammatory responses. This review highlights the role of T cells and integrins in the inflammatory process involved in the pathophysiology of DED and outlines the scientific rationale for the role of lifitegrast. In addition, the preclinical development, pharmacological properties, clinical efficacy, and safety of lifitegrast are described.

KEY WORDS dry eye disease, ICAM-1, inflammation, integrin antagonist, LFA-1, lifitegrast

I. INTRODUCTION

Dry eye disease (DED; also referred to as keratoconjunctivitis sicca or dry eye syndrome) is a multifactorial disorder, characterized by either decreased tear production or increased tear film evaporation,[1] which affects both the ocular surface and the lacrimal gland. Although its pathogenesis is not yet fully elucidated, DED is now recognized as a disease associated with ocular surface inflammation.[1] Indeed, the infiltration of T cells in the lacrimal functional unit, including the conjunctiva and lacrimal glands, is known to result in chronic inflammation.

The role of T cells is pivotal in the development of cell-mediated immune responses. More specifically, CD4 positive (+) T helper (T_H) 1 and T_H17 T cells have been identified as mediators of ocular surface inflammation in DED.[2] Recruitment and activation of these T cells at the ocular surface lead to the release of effector cytokines and contribute to the ocular tissue damage seen in patients with DED. In fact, proinflammatory cytokines have been detected in the tear film of patients with DED.[3,4] Therefore, it is hoped that therapies targeting T cells will provide a more efficient means to treat DED.

Currently available treatments include immunomodulators and immunosuppressive agents (e.g., ophthalmic cyclosporine [Restasis®][5] and ophthalmic corticosteroids).[1] Ophthalmic cyclosporine is presently the only approved prescription therapy for use in patients with DED in the United States and Canada. Despite the progress made in recent years in the understanding of the pathophysiology of DED, there is at present no single on- or off-label medication that displays all the following characteristics and benefits of an ideal DED agent: 1) exhibits good tolerability and long-term safety, 2) has a rapid onset of action, 3) targets key steps of the inflammation cycle, and, most importantly, 4) treats both signs and symptoms of DED. Thus, there is an unmet need for new and effective DED therapies, and the recent focus of drug development has been to find novel compounds targeting inflammation.

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OUTLINE

Abbreviations

+	Positive
APC	Antigen-presenting cell
CYP450	Cytochrome P450
DED	Dry eye disease
IC^{50}	Half maximal inhibitory concentration
ICAM-1	Intercellular adhesion molecule 1
ICSS	Inferior corneal staining score
IFN	Interferon
IL-1	Interleukin 1
IS	Immunological synapse
LFA-1	Lymphocyte function-associated antigen 1
MMP	Matrix metalloproteinase
PK	Pharmacokinetic
SD	Standard deviation
T_H	T helper cell
TNF	Tumor necrosis factor
Treg	Regulatory T cell

Lifitegrast is a novel small molecule integrin antagonist that inhibits a specific T cell-mediated inflammatory pathway involved in the pathogenesis of DED. Based on the current understanding of its mechanism of action, lifitegrast blocks the recruitment and activation of T cells to the ocular surface, thus lessening overall inflammatory responses. If approved, lifitegrast has the potential to be the first treatment indicated to treat both signs and symptoms of DED.

Herein, we review the role of T cells and integrins in the inflammatory process involved in the pathophysiology of DED and outline the scientific rationale for the role of lifitegrast. In addition, the preclinical development, pharmacological properties, clinical efficacy, and safety of lifitegrast are described.

II. ROLE OF T CELLS, INTEGRINS, AND ADHESION LIGANDS IN THE INFLAMMATORY PROCESS AND DRY EYE DISEASE

A. Immunology of DED

The pathology of DED is not yet fully understood, but there is growing evidence that T cell-mediated inflammation plays a central role in the disease.[6,7] The role of T cells in DED involves the following 6 steps: 1) uptake and processing of antigens from the ocular tissue by antigen-presenting cells (APC) on the ocular surface, 2) priming of T cells by APCs in the lymphoid compartment, 3) migration of T cells through the blood vessels, 4) recruitment of T cells to the conjunctival stroma, 5) activation of T cells, and 6) retention of T cells into inflamed tissues, as illustrated in Figure 1. Specifically, when desiccating environmental stress is applied to the ocular surface, it induces tear hyperosmolarity and the release of proinflammatory cytokines (e.g., interleukin [IL]-1 and tumor necrosis factor [TNF]-α) via activated kinases.[8] This proinflammatory milieu promotes the activation and maturation of APCs. The migration of mature APCs to lymph nodes in turn triggers the generation of autoreactive CD4+ T cells[6] that journey to the ocular surface, where additional cytokines are produced, thus causing further damage to the corneal epithelium and conjunctival cells (Figure 1).

Understanding the mechanisms involved in the onset and progression of DED is key to the successful development of effective therapeutic interventions. A number of investigational studies and animal models of DED have helped identify and quantify the T cell subtypes and biomarkers (e.g., cytokines, chemokines, and ILs) of ocular inflammation that are implicated in DED. CD4+ T cells, which are found in ocular surface tissues of patients with DED, are the primary infiltrating cells involved in DED.[2,9,10] CD4+ T cells can differentiate via divergent pathways into 4 distinct subsets of T cells, namely T_H1, T_H2, T_H17, and regulatory T cells (Treg), depending on which stimuli are driving the onset of inflammation.[11]

Recent human and experimental murine dry eye studies showed that a T_H1- and T_H17-mediated immune response is induced in the lymphoid compartment upon engagement with mature APCs,[4,9,12] as depicted in Figure 1. T_H1 and T_H17 cells subsequently migrate to the ocular surface, where they secrete additional markers of inflammation, in particular interferon (IFN)-γ and IL-17, respectively.[3,4] These cytokines in turn promote the production and release of various proinflammatory mediators (including cytokines, chemokines, and matrix metalloproteinases [MMPs]) by the conjunctival and corneal epithelium, thus creating a self-perpetuating cycle of inflammation. Relative contributions of T_H1 and T_H17 cells to the pathogenesis of DED are not fully understood, but evidence suggests that IFN-γ causes conjunctival goblet cell loss and apoptosis of the ocular surface epithelium,[5] while IL-17 stimulates the production of MMPs that cause breakdown of the corneal epithelial barrier.[4] When damaged, the corneal epithelium allows greater access of pathogens and inflammatory mediators to the corneal epithelium and stroma (Figure 1), events that may lead to decreased visual function for patients with DED.[12]

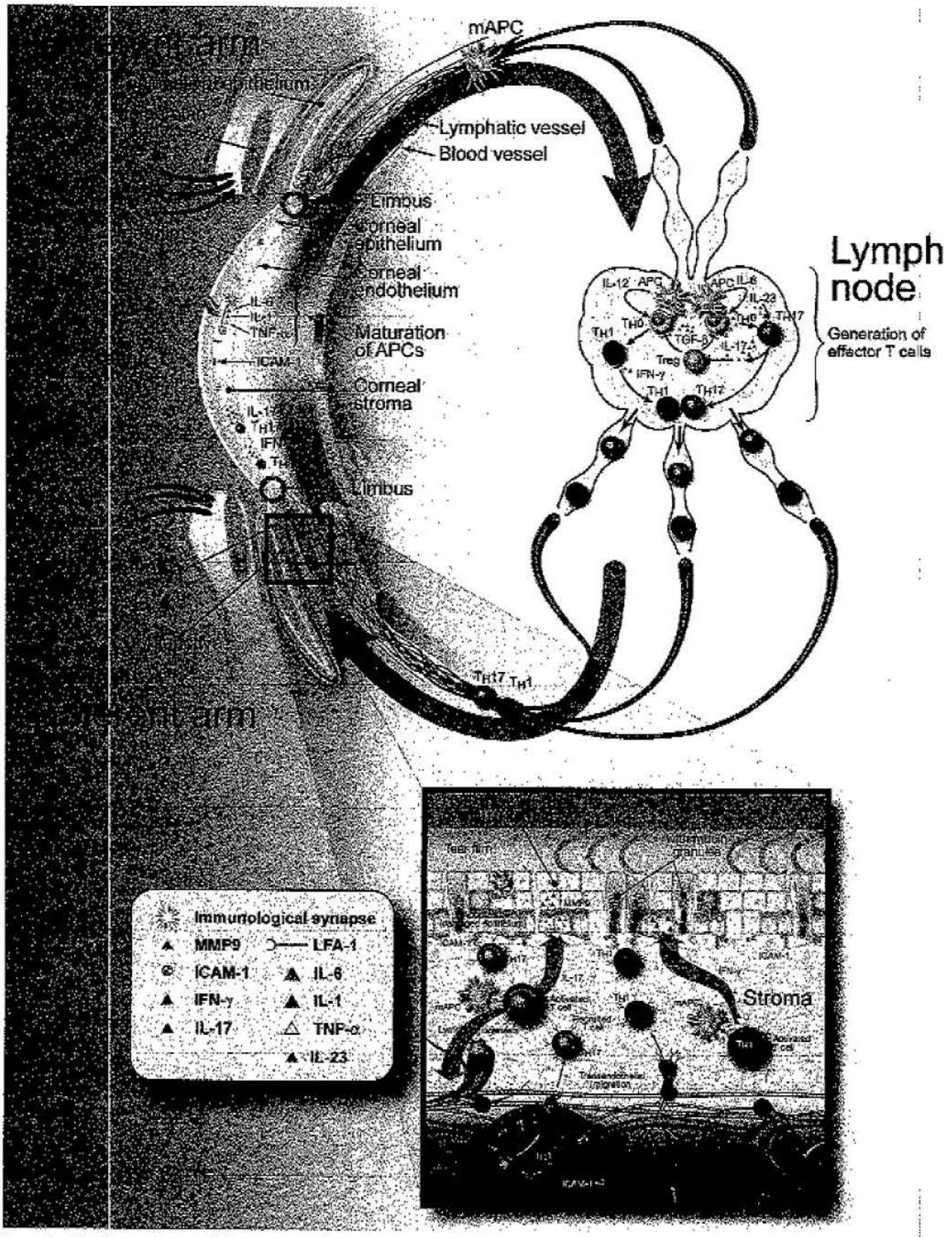

Figure 1. The dry eye immunoinflammatory pathway. APC = antigen-presenting cell; ICAM-1 = intercellular adhesion molecule 1; IFN = interferon; IL = interleukin; LFA-1 = lymphocyte function-associated antigen 1; mAPC = mature antigen-presenting cell; MMP = matrix metalloproteinase; T_H = T helper cell; TNF = tumor necrosis factor; Treg = regulatory T cell.

Taken together, these findings support the idea that inhibiting T cell recruitment and activation by APCs during the development of the inflammatory response in DED should result in decreased levels of pathogenic mediators and less inflammation on the ocular surface.

B. Integrin Signaling in the Immunoinflammatory Pathway

Integrins are cell surface receptors involved in the integration between extracellular and intracellular signals in many biological processes, including cytoskeletal organization and cell adhesion, migration, proliferation, differentiation, and survival.[13] During an immune response, integrins mediate 1) cell adhesion to the extracellular matrix, and 2) cell-cell interactions (e.g., T cell activation), which are central to the pathology of many inflammatory diseases, including DED (Figure 1).

Naïve and memory T cells circulate freely in blood vessels, monitoring for foreign antigens. Integrins are specific heterodimeric receptors used by T cells to routinely migrate in and out of lymph nodes when unchallenged, or into other tissues following activation by an inflammatory signal.[14] At the beginning of an immune response, T cells need to be able to access the site of inflammation by crossing the vascular endothelium of blood vessels. This process is enabled by a specific integrin expressed on T cells and termed lymphocyte function-associated antigen 1 (**LFA-1**), $\alpha_L\beta_2$, or CD11a/CD18, through binding to its native ligand, intercellular adhesion molecule 1 (**ICAM-1**). The expression of LFA-1 is restricted to leukocytes, and LFA-1 is 1 of 12 integrins (out of the 24 known[15]) used by T cells to direct their movement and function.[14]

ICAM-1, an adhesion protein expressed on a variety of cells including APCs and endothelial cells, was first proven to be a ligand for LFA-1 in 1987 by Marlin and Springer.[16] This discovery, together with additional studies, established the understanding of the LFA-1/ICAM-1 pair as a key adhesion pathway in T cell-mediated inflammation.[17,18] Specifically, the interaction of LFA-1 with ICAM-1 is important not only for T cell adhesion to endothelial cells before transendothelial migration to inflamed tissues, but also for T cell interaction with APCs. At the site of inflammation, T cells come into contact with APCs. Upon antigen presentation and recognition, key receptors at the cell-cell interface reorganize to enable the formation of an immunological synapse (**IS**), which stabilizes once ICAM-1, expressed on APCs, is bound to LFA-1.[19,20] The mature IS in turn helps sustain the otherwise transient interaction between the T cell and the APC, which facilitates the propagation of downstream proinflammatory factors, from the T cells themselves and from other bystander cells (Figure 1). In the ocular surface, T cells and corneal epithelial cells produce these signals (e.g., IFN-γ, IL-17, TNF-α, IL-1) accordingly.

TNF-α and IL-1 are known to amplify the inflammatory response by inducing the expression of ICAM-1 on epithelial cells in patients with DED.[21,22] LFA-1 also is upregulated in the conjunctiva of patients with DED.[23] The presence of excess ICAM-1 acts as an activating signal for patrolling T cells in the conjunctival and corneal tissues. It drives the recruitment of additional T cells to the ocular surface through increased LFA-1 expression, thus contributing to the perpetuation of inflammation. Based on the current understanding of DED, blocking the LFA-1/ICAM-1 interaction could be a viable strategy for the prevention and treatment of ocular surface inflammation.

Targeting integrin signaling has been shown to be a valid drug discovery strategy and has allowed the development of drugs with potent anti-inflammatory activities in various autoimmune/inflammatory diseases.[13] For example, efalizumab (Raptiva®),[24] a recombinant humanized monoclonal immunoglobulin G1 antibody against the α subunit of LFA-1 (anti-CD11a), was one of the first integrin antagonists to be marketed for the treatment of moderate to severe psoriasis.[15] It was designed to bind to LFA-1 and block its function in T cell activation in lymph nodes, T cell adhesion and extravasation to inflamed skin, and T cell reactivation in the skin by APCs.[25] Natalizumab (Tysabri®)[26] is another approved drug (for the treatment of relapsing forms of multiple sclerosis) that targets an integrin pathway, specifically the α4-integrin subunit.[27] Targeting integrin signaling systematically can increase the risk of certain rare infections, a side effect that would not be anticipated in a topical medication that reaches systemic circulation at extremely low levels and then is rapidly excreted. Additionally, because lifitegrast is a small molecule antagonist to a specific amino acid sequence of ICAM-1 and not an antibody, it is expected that associated side effects will be minimal.

Preclinical studies in various ocular diseases have shown that inhibiting the interaction between integrins and their ligands, particularly LFA-1 and ICAM-1, holds promise as a therapeutic approach. In a mouse model of induced allergic conjunctivitis, it was established that the greatest inhibition of cellular infiltration in the conjunctiva was achieved with the treatment combination of anti-LFA-1 and anti ICAM-1 monoclonal antibodies,[28] compared with monotherapy with either antibody. In murine endotoxin-induced uveitis, a model for acute inflammation, Becker et al observed a reduced number of infiltrating leukocytes in animals receiving neutralizing antibodies for either LFA-1 or ICAM-1.[29]

These preclinical studies constitute proof-of-concept evidence for targeting integrin signaling in order to reduce ocular surface inflammation. At the time these discoveries were made, it became apparent to experts in the field that if a small molecule that blocked the interaction between LFA-1 and ICAM-1 could be developed, it had the potential to translate into clinical use.

III. DEVELOPMENT OF LIFITEGRAST, AN INTEGRIN ANTAGONIST, AS A TREATMENT FOR DRY EYE DISEASE

Lifitegrast is a novel small molecule integrin antagonist that blocks the binding of ICAM-1 to LFA-1, thus interrupting the T cell-mediated inflammatory cycle.

A. Discovery and Development of Lifitegrast

Protein-protein interactions are central to a majority of biological processes, and are challenging targets to tackle with small molecule inhibitors.[30] These interfaces are large, complex, and difficult to disrupt because of flat surfaces or less-defined binding sites.

In 2002, Gadek et al described the identification of a new series of ICAM-1 mimics and LFA-1 antagonists.[31] It was hypothesized that ICAM-1 could act as a drug discovery lead in the generation of small molecule therapeutics, and the authors succeeded in transferring the binding epitope of ICAM-1 to a small molecule framework. By examining a whole host of molecules through combinatorial chemistry and structure-activity relationship, Gadek et al demonstrated that a molecule coded as Compound 4 (Figure 2) directly inhibited the association of LFA-1 with ICAM-1 by binding to a high-affinity site on LFA-1 (I domain of the α_L subunit).

Between 2010 and 2012, Zhong et al reported the discovery and development of a potent tetrahydroisoquinoline class of LFA-1/ICAM-1 antagonists,[32-34] from which lifitegrast[35] (Compound 1g in Zhong et al[32]; Figure 2) was identified as a promising drug candidate. The central tetrahydroisoquinoline moiety was designed to retain potency of binding affinity to LFA-1.

B. Mechanism of Action of Lifitegrast at the Molecular and Cellular Levels

Based on earlier work on putative ICAM-1 mimics and LFA-1 antagonists (including Compound 4) by Gadek et al[31] and pre-discovery and development of lifitegrast, it has been hypothesized that these molecules bind directly to the ICAM-1 binding site on the I domain of the LFA-1 α_L subunit and act as direct competitive antagonists to block ICAM-1 binding.[36] Alternative attempts to determine the mechanism of inhibition of these compounds (including Compound 4) via surface plasmon resonance experiments suggested that these molecules might not be ligand mimetics of ICAM-1, but that they instead bind to the I-like domain of the LFA-1 β_2 subunit in an allosteric fashion.[37] The mechanism of action of lifitegrast (and other putative ICAM-1 mimics and LFA-1 antagonists) was still under debate until recently. At international congresses in 2013 and 2014, Semba et al reported additional findings on lifitegrast itself, supporting the compound as a direct competitive antagonist of the binding of ICAM-1 to LFA-1 (personal communication, July 2015). In a live-cell experiment[38] created to mimic the binding of LFA-1 to ICAM-1, it was found that lifitegrast inhibited the formation and activation of the IS by affecting LFA-1/ICAM-1 adhesion and by outcompeting ICAM-1 binding to LFA-1 in a dose-dependent fashion. These results confirmed earlier in vitro work demonstrating the ability of lifitegrast to inhibit the attachment of Jurkat T cells to ICAM-1.[39]

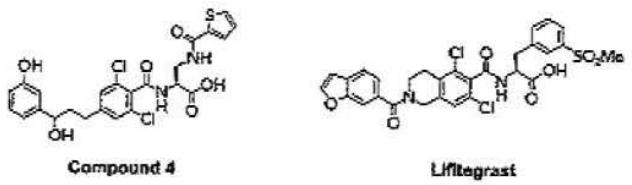

Figure 2. Molecular structures of Compound 4[31] and lifitegrast.[32]

Lifitegrast inhibits the LFA-1/ICAM-1 interaction and as a result should block the subsequent cycle of T cell-mediated inflammation (Figure 3). Lifitegrast's downstream effect on cytokines has been reported in multiple preclinical studies. The drug has been shown to reduce corneal inflammation in mice by inhibiting neutrophil recruitment to the corneal stroma,[40] and to inhibit cytokine release from activated lymphocytes in vitro.[39] Specifically, the inhibitory effect of lifitegrast was significant at 1 μM for IFN-γ, IL-1β, IL-10, and macrophage inflammatory protein 1α, cytokines and chemokines whose presence in tears correlates with the clinical severity of DED.[41] In the phase I clinical study,[42] Semba et al showed that tear concentrations of lifitegrast in healthy volunteers reached, and in some instances exceeded, the target ocular therapeutic level of >1 μM. Additionally, administration of lifitegrast was found to be efficacious in 12 dogs of various breeds, all prone to develop spontaneous keratoconjunctivitis sicca.[39] This body of preclinical evidence confirmed potent dose-dependent inhibition of lifitegrast on the T cell activation, T cell recruitment, and cytokine release steps in the inflammatory process (Figure 3), thus suggesting that treatment with lifitegrast should decrease the inflammatory response and reduce levels of proinflammatory mediators in patients with DED.

C. Lifitegrast: An Ophthalmic Agent for Treatment of Dry Eye Disease

Topical administration is a minimally invasive therapy for patients and has the advantage of increasing the selectivity of a drug for its intended target. Nevertheless, delivering a drug to a specific site of action in the eye is still a challenge for scientists. Lifitegrast was rationally designed and developed to be topically administered as an ophthalmic solution for treating DED. The compound was thus engineered to have a favorable pharmacokinetic (PK) profile in the eye, with the following properties:

1) *Strong inhibition of T cell adhesion to ICAM-1 expressing surfaces.* Zhong et al demonstrated that lifitegrast was potent in T cell adhesion assays, including the HUT 78 T cell adhesion assay (half maximal inhibitory concentration [IC_{50}] = 9 nM).[32] Murphy et al showed that lifitegrast strongly inhibited Jurkat T cell attachment to ICAM-1 (IC_{50} = 2.98 nM),[39] thus confirming that lifitegrast inhibits the recruitment of T cells.
2) *High solubility in aqueous media.*[32] Together with drug permeability, solubility is one of the important parameters that helps achieve desired drug concentrations within targeted ocular tissues. Several techniques exist to enhance solubility of a drug compound in aqueous media, including chemical

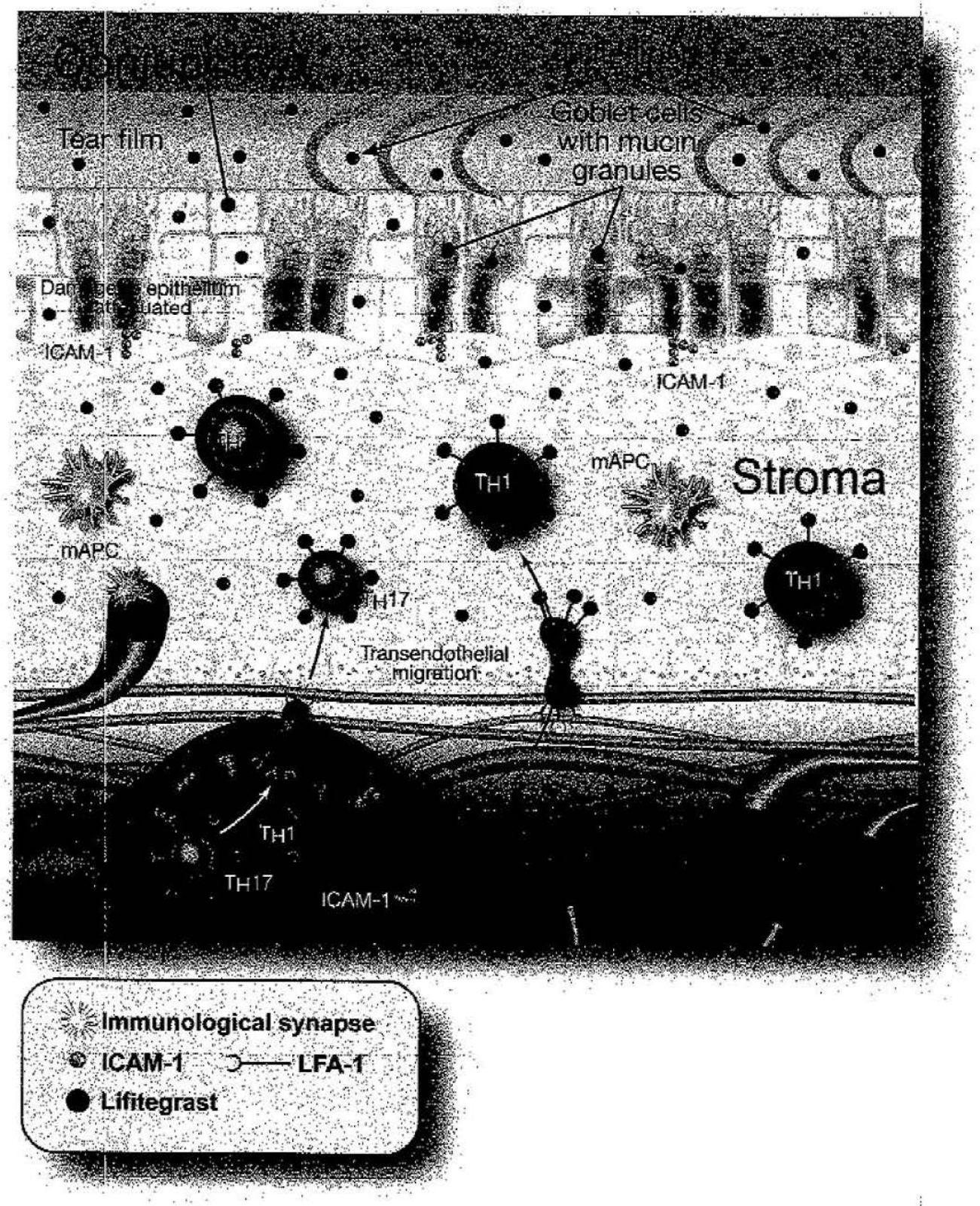

Figure 3. Mechanism of action (MOA) of lifitegrast at the cellular level. ICAM-1 = intercellular adhesion molecule 1; LFA-1 = lymphocyte function-associated antigen 1; mAPC = mature antigen-presenting cell; T_H = T helper cell. Disclaimer: this figure illustrates the current understanding of the MOA of lifitegrast based on completed preclinical and clinical studies. Additional studies in the posterior ocular tissues and vascular system are required to further elucidate the MOA of lifitegrast.

modification by formation of a salt.[43] Lifitegrast is formulated as a sodium salt, which allows for concentrations of ≤100 mg/ml (10%) to be isotonic with human tears at ~300 mOsmol/l. Lifitegrast dosing strengths of ≤50 mg/ml (5.0%) have been used in animal and human studies to maintain the ophthalmic solution at physiological pH.[32] The lifitegrast formulation currently under development for the treatment of DED is a preservative-free 5.0% solution and as such, the product is provided in single-unit dose vials. Lifitegrast's formulation is preservative free in order to minimize aggravation of dry eye that can be caused by such additives.[44]

3) *Rapid absorption into ocular tissues.* Animal models have shown that greater rates of drug penetration and delivery across barriers can be achieved as a result of lifitegrast's high intrinsic solubility and good permeability. The ocular PK of lifitegrast was determined by radiolabeled experiments in rats[45] and dogs.[39] Therapeutic levels of the drug were observed in all ocular tissues, specifically in the bulbar conjunctiva, palpebral conjunctiva, cornea, aqueous humor, vitreous humor, and sclera, 30 min after a single topical ocular administration of ^{14}C-lifitegrast.[45] Ocular penetration also was investigated in dogs, and this has confirmed previous findings.[39] Concentrations of radioactivity were determined to be the highest in the anterior tissues (bulbar conjunctiva, palpebral conjunctiva, and cornea) 30 min post topical dosing. In the human diseased eye, the corneal epithelium and stroma act as barriers between intraocular tissues and the vascular system, thus limiting the permeation of topically administered ophthalmic drugs.[46] In animals, drug levels in ocular tissues can be determined directly through harvesting of the eyes, unlike in humans. Serum plasma concentrations of lifitegrast, determined from patient blood samples, are an indirect measure of the drug's ability to penetrate ocular tissues. Indeed, once a drug accesses posterior ocular tissues, which are highly vascularized, it is subjected to vascular absorption and clearance into the systemic circulation. Peak plasma concentrations of lifitegrast in subjects receiving a single drop of the 5.0% formulation in the phase I clinical trial were detected within 5 min of topical delivery in the eye,[42] thus confirming the rapid absorption of lifitegrast into human ocular tissues.

4) *Rapid clearance from the systemic circulation.* Rat intravenous PK experiments showed a short half-life (0.78 h), high clearance (139.2 ml/min/kg) and low systemic exposure (area under the concentration curve = 705 h*ng/kg) for lifitegrast.[32] This was confirmed in the phase I study in healthy subjects, which established that low plasma levels of lifitegrast were cleared within 1-4 hours of dosing.[42] Additionally, lifitegrast was shown to have good metabolic stability in vitro in both human and rat liver microsomes (71% and >95%, respectively, after 30 min incubation), which contain various drug-metabolizing enzymes including cytochrome P450 (CYP450) enzymes.[32] CYP450 enzymes are primarily found in the liver, but they are known to be present in corneal tissues and to participate in drug detoxification.[47,48]

5) *Good safety profile in vitro and in vivo.*[32] The compound was shown to be negative in the Ames test, an assay used to determine whether a chemical can cause mutations in the DNA of the test species (in this instance, bacteria strains). Lifitegrast had low potency in the CYP450 inhibition assay (CYP3A4 [one of the major isoforms], IC_{50} >20 μM; CYP2C9, IC_{50} = 3.0 μM), which tests whether a chemical can affect the activity of CYPs and thus potentially alter drug metabolism in patients,[49] thereby causing therapeutic inefficacy or unanticipated adverse reactions. Additionally, lifitegrast exhibited low potency in the human *ether-à-go-go*-related gene assay (patch clamp, IC_{50} >20 μM), which tests whether a chemical can cause torsades de pointes, thus predisposing a patient to sudden cardiac death. The phase I clinical study in normal healthy adults[42] confirmed that lifitegrast was well tolerated when administered in single and multiple ascending doses. Specifically, subjects did not experience any clinically meaningful changes in their health assessments (vital signs, electrocardiogram, and complete ophthalmologic exam).

In summary, lifitegrast is optimized for ocular use, with an excellent PK profile and a very low systemic exposure. Hence, it is expected to work effectively in the human eye without systemic side effects.

Lifitegrast is currently in late phase III development. The lifitegrast clinical development program is the largest of its kind; it began in 2008 and has enrolled >1,800 patients with DED (placebo and lifitegrast groups). Four clinical studies (3 efficacy and safety studies and 1 long-term exposure safety study) have been completed to date, with further research in progress. Evidence of the efficacy and safety of lifitegrast in patients with DED has been observed in the following clinical studies, which were carried out exclusively in the United States.

In a phase II clinical study (ClinicalTrials.gov identifier, NCT00926185),[50] the group of subjects treated with lifitegrast ophthalmic solution 5.0% did not show a statistically significant difference from the placebo group for the single primary efficacy endpoint (sign), mean inferior corneal staining score (ICSS) at day 84 (last visit, week 12). A prespecified secondary sign endpoint, mean (standard deviation, SD) change in ICSS from baseline to day 84 (from week 0 to week 12), showed a significant response for the lifitegrast ophthalmic solution 5.0% group compared with placebo (0.05 [0.773] vs 0.40 [0.802], P=.021). Significant improvements in a prespecified secondary symptom endpoint (change on the visual-related function subscale

of a symptom scale) also were noted from baseline to day 84 in the lifitegrast group compared with placebo (−0.30 [0.934] vs 0.07 [0.929], P=.039).[50]

Following the promising findings in the phase II study, the OPUS-1 phase III clinical study (ClinicalTrials.gov identifier, NCT01421498)[51] was conducted between 2011 and 2012, with coprimary objective (sign) and subjective (symptom) efficacy endpoints. Analysis of study results showed that the mean (SD) change from baseline to day 84 in ICSS was greater in the lifitegrast ophthalmic solution 5.0% group compared with placebo (−0.07 [0.868] vs 0.17 [0.819], P<.001). The symptom coprimary endpoint (change on the visual-related function subscale) was not met in this study. However, improvements were noted at day 84 in ocular discomfort in the lifitegrast group compared with placebo (1.10 [1.153] vs 1.31 [1.182], P=.027) and eye dryness in the lifitegrast group compared with placebo (25.00 [28.870] vs 30.39 [30.773], P=.029).[51]

The OPUS-2 phase III clinical study (ClinicalTrials.gov identifier, NCT01743729)[52] was conducted between 2012 and 2013, with coprimary sign and symptom efficacy endpoints. Study results showed that subjects treated with lifitegrast ophthalmic solution 5.0% experienced greater improvement in eye dryness score (mean [SD] change from baseline to day 84) than subjects treated with placebo (−35.30 [28.400] vs −22.75 [28.600], P<.001). Additionally, nominally significant improvements were noted in the secondary symptom endpoints ocular discomfort in the lifitegrast group compared with placebo (−0.91 [1.280] vs −0.57 [1.354], nominal P<.001), and eye discomfort in the lifitegrast group compared with placebo (−26.46 [31.328] vs −16.73 [31.207], nominal P<.001). The sign coprimary endpoint (mean change from baseline to day 84 in ICSS) was not met in this study.[52] In the phase II, OPUS-1 and OPUS-2 studies, lifitegrast was generally well tolerated and there were no serious ocular treatment-emergent adverse events.

The SONATA long-term safety study (ClinicalTrials.gov identifier, NCT01636206) of lifitegrast ophthalmic solution 5.0% is completed. Results from this study were presented at congresses in 2015 and provided further evidence of the safety of lifitegrast. Full results will be published separately. The OPUS-3 phase III clinical study (ClinicalTrials.gov identifier, NCT02284516) is completed. Results will be published separately.

IV. CONCLUSION

Integrin inhibitors have been found to have potent anti-inflammatory effects in several autoimmune/inflammatory diseases. Targeting specific inflammation steps, including integrins and cytokines, is a promising avenue for the development of new and effective therapeutic interventions in DED. Lifitegrast is a novel integrin antagonist specifically developed to target the LFA-1 (an integrin) and ICAM-1 (an intercellular adhesion molecule) interaction. Lifitegrast inhibits T cell recruitment, T cell activation, and subsequent cytokine release, thereby targeting a specific inflammatory pathway involved in the pathogenesis of DED.

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