

TO:

State of Alaska
Members of the Pharmacy and Therapeutics Committee

ATTN: John McCall R-Ph

Fax

To: John McCall R-Ph

From: SHIRE

Fax Number: 907-561-1684

15 Pages (including cover sheet)

Phone:

Date: 10/17/2016

Re: XIIDRA (lifitegrast ophthalmic solution)

5%

CC:

Urgent For Review Please Comment Please Reply Please Recycle

NOV 18th 2016 AGENDA REQUEST FOR PRESENTATION AND P&T CLINICAL REVIEW OF XIIDRA (lifitegrast ophthalmic solution) 5%

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 **DATE:** 1 0 - 1 7 - 2 0 1 6

PRODUCT MANAGER'S NAME: **TITLE:**

ADDRESS:
300 SHIRE WAY

CITY: LEXINGTON **STATE:** M A **ZIP CODE:** 0 2 4 2 1

PHONE NUMBER: 6 1 7 - 3 4 9 - 0 2 0 0 **FAX NUMBER:**

PRODUCT:
XIIDRA (lifitegrast ophthalmic solution) 5%

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

XIIDRA is the only prescription eye drop FDA-approved to treat both the signs and symptoms of Dry Eye Disease



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIIDRA safely and effectively. See full prescribing information for XIIDRA.

XIIDRA™ (lifitegrast ophthalmic solution) 5%, for topical ophthalmic use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

DOSAGE AND ADMINISTRATION

One drop twice daily in each eye (approximately 12 hours apart). (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing lifitegrast 5% (50 mg/mL). (3)

CONTRAINDICATIONS

None (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence 5-25%) following the use of Xiidra were instillation site irritation, dysgeusia and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling.

Revised: 07/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xiidra™ (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

2 DOSAGE AND ADMINISTRATION

Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single use container. Discard the single use container immediately after using in each eye.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing lifitegrast 5% (50 mg/mL).

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25 % of patients were instillation site irritation, dysgeusia and reduced visual acuity.

Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear [see *Clinical Pharmacology* (12.3)].

Data

Animal Data

Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low [see *Clinical Pharmacology* (12.3)]. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

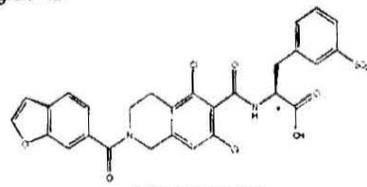
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11 DESCRIPTION

The chemical name for lifitegrast is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. The molecular formula of lifitegrast is C₂₉H₂₄Cl₂N₂O₇S and its molecular weight is 615.5. The structural formula of lifitegrast is:



* Chiral center

Lifitegrast is a white to off-white powder which is soluble in water.

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist supplied as a sterile, clear, colorless to slightly brownish-yellow colored, isotonic solution of lifitegrast with a pH of 7.0–8.0 and an osmolality range of 200–330 mOsmol/kg.

Xiidra contains **Active:** lifitegrast 50 mg/mL; **Inactives:** sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in dry eye disease. LFA-1/ICAM-1 interaction can contribute to the formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies demonstrated that lifitegrast may inhibit T-cell adhesion to ICAM-1 in a human T-cell line and may inhibit secretion of inflammatory cytokines in human peripheral blood mononuclear cells. The exact mechanism of action of lifitegrast in dry eye disease is not known.

12.3 Pharmacokinetics

In a subset of dry eye disease patients (n=47) enrolled in a Phase 3 trial, the pre-dose (trough) plasma concentrations of lifitegrast were measured after 180 and 360 days of topical ocular dosing (1 drop twice daily) with Xiidra (lifitegrast ophthalmic solution) 5%. A total of nine (9) of the 47 patients (19%) had plasma lifitegrast trough concentrations above 0.5 ng/mL (the lower limit of assay quantitation). Trough plasma concentrations that could be quantitated ranged from 0.55 ng/mL to 3.74 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis

Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of fertility

Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose (RHOD) of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

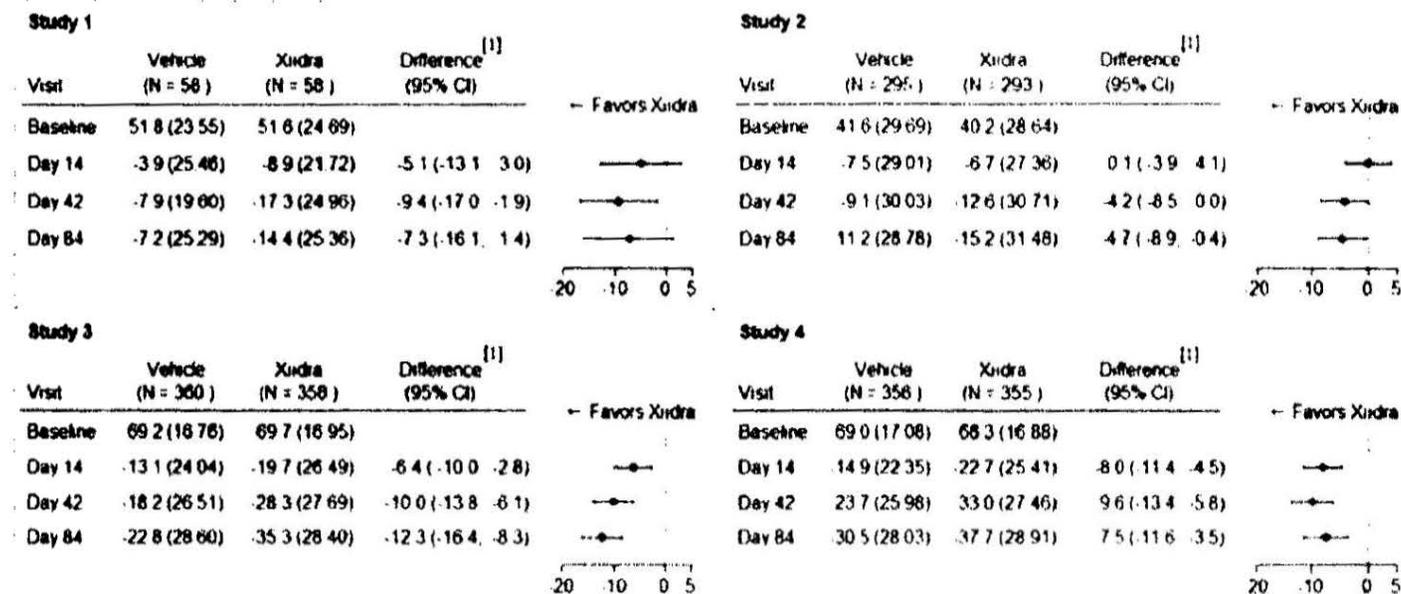
14 CLINICAL STUDIES

The safety and efficacy of lifitegrast for the treatment of dry eye disease were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multi-center, double-masked, vehicle-controlled studies. Patients were randomized to Xiidra or vehicle (placebo) in a 1:1 ratio and dosed twice a day. Use of artificial tears was not allowed during the studies. The mean age was 59 years (range, 19–97 years). The majority of patients were female (76%). Enrollment criteria included, minimal signs (i.e., Corneal Fluorescein Staining (CFS) and non anesthetized Schirmer Tear Test (STT)) and symptoms (i.e., Eye Dryness Score (EDS) and Ocular Discomfort Score (ODS)) severity scores at baseline.

Effects on Symptoms of Dry Eye Disease

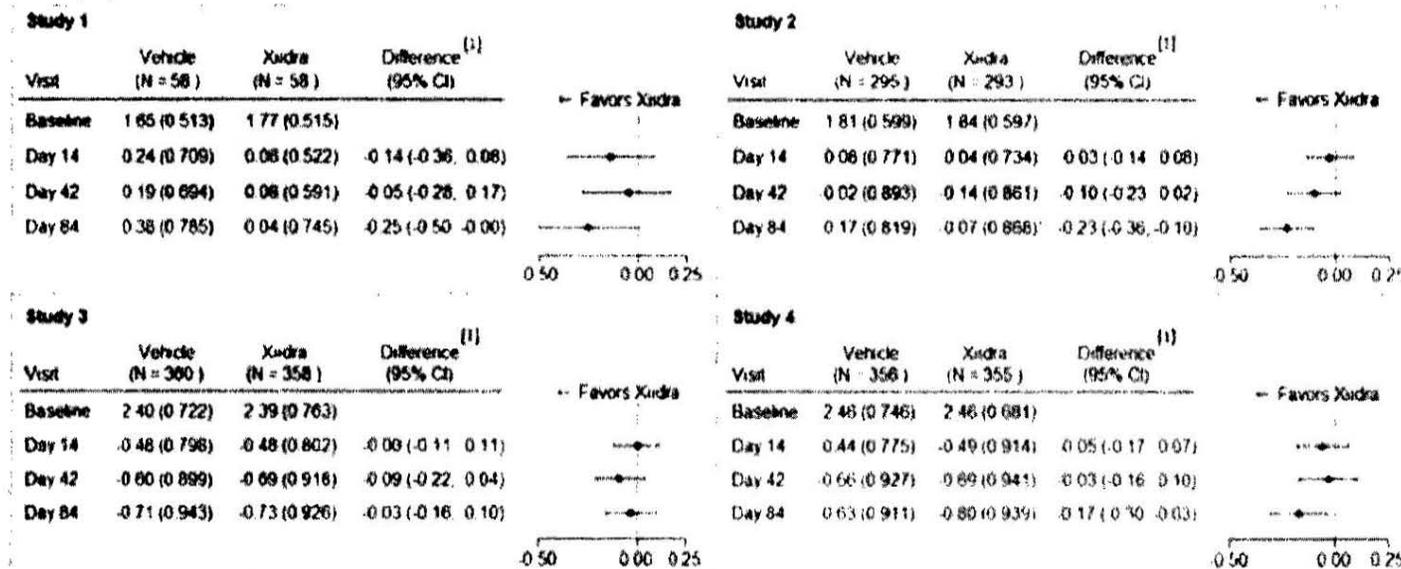
Eye dryness Score (EDS) was rated by patients using a visual analogue scale (VAS) (0 = no discomfort, 100 = maximal discomfort) at each study visit. The average baseline EDS was between 40 and 70. A larger reduction in EDS favoring Xiidra was observed in all studies at Day 42 and Day 84 (see Figure 1).

Figure 1: Mean Change (SD) from Baseline and Treatment Difference (Xiidra – Vehicle) in Eye Dryness Score in 12-Week Studies in Patients with Dry Eye Disease



[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. In Study 1, one Xiidra treated subject who did not have a baseline value was excluded from analysis.

Figure 2: Mean Change (SD) from Baseline and Treatment Difference (Xiidra – Vehicle) in Inferior Corneal Staining Score in 12-Week Studies in Patients with Dry Eye Disease.



[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. In Study 2, one Vehicle treated subject who did not have a study eye designated was excluded from analysis.

Effects on Signs of Dry Eye Disease

Inferior fluorescein corneal staining score (ICSS) (0 = no staining, 1 = few/rare punctate lesions, 2 = discrete and countable lesions, 3 = lesions too numerous to count but not coalescent, 4 = coalescent) was recorded at each study visit. The average baseline ICSS was approximately 1.8 in Studies 1 and 2, and 2.4 in Studies 3 and 4. At Day 84, a larger reduction in ICSS favoring Xiidra was observed in three of the four studies (see Figure 2).

16 HOW SUPPLIED/STORAGE AND HANDLING

Xiidra (lifitegrast ophthalmic solution) 5% (50 mg/mL) is supplied in a foil pouch containing 5 low density polyethylene 0.2 mL single use containers. NDC 54092-606-01; Carton of 60 single use containers.

Storage:

Store at 20-25°C (68-77°F). Store single use containers in the original foil pouch.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling.

Handling the Single Use Container

Advise patients not to touch the tip of the single use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

Use with Contact Lenses

Advise patients that contact lenses, should be removed prior to administration of Xiidra and can be reinserted 15 minutes after administration [see Dosage and Administration (2)].

Administration

Advise patients that the solution from one single use container is to be used immediately after opening. It can be used to dose both eyes. The single use container, including any remaining contents should be discarded immediately after administration [see Dosage and Administration (2)].

Storage Information

Instruct patients to store single use containers in the original foil pouch until ready to use.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421

For more information, go to www.Xiidra.com or call 1-800-828-2088.

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US Patents: 8367701; 9353088; 7314938; 7745460; 7790743; 7928122; 9216174; 8168655; 8084047; 8592450; 9085553 and pending patent application.

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Patient Information
Xiidra™ (ZYE-druh)
(lifitegrast ophthalmic solution) 5%

What is Xiidra?

Xiidra is a prescription eye drop solution used to treat the signs and symptoms of dry eye disease. It is not known if Xiidra is safe and effective in children under 17 years of age.

Before you use Xiidra, tell your doctor if you:

- are using any other eye drops
- wear contact lenses
- are pregnant or plan to become pregnant. It is not known if Xiidra will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Xiidra passes into your breast milk. Talk to your doctor about the best way to feed your baby if you use Xiidra.

How should I use Xiidra?

See the complete Instructions for Use at the end of this Patient Information leaflet for detailed instructions about the right way to use Xiidra.

- Use Xiidra as your doctor tells you.
- Use 1 drop of Xiidra in each eye, 2 times each day, about 12 hours apart.
- Use Xiidra right away after opening. Throw away the single use container and any unused solution after you have applied the dose to both eyes. Do not save any unused Xiidra for later.

What are the possible side effects of Xiidra?

The most common side effects of Xiidra include eye irritation, discomfort, or blurred vision when the drops are applied to the eyes, and an unusual taste sensation (dysgeusia).

Tell your doctor if you have any side effects that bother you. These are not all the possible side effects of Xiidra.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Xiidra?

- Store Xiidra at room temperature between 68°F to 77°F (20°C to 25°C).
- Store Xiidra in the original foil pouch to protect it from light.
- Do not open the Xiidra foil pouch until you are ready to use the eye drops.
- Return unused single use containers to their original foil pouch to protect from excessive light exposure.

Keep Xiidra and all medicines out of the reach of children.

General information about the safe and effective use of Xiidra.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or doctor for information about Xiidra that is written for health professionals. Do not use Xiidra for a condition for which it was not prescribed. Do not give Xiidra to other people, even if they have the same symptoms you have. It may harm them.

What are the ingredients in Xiidra?

Active ingredient: lifitegrast

Inactive ingredients: sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

**Manufactured for: Shire US Inc., 300 Shire Way,
Lexington, MA 02421**

**For more information, go to www.Xiidra.com or call
1-800-828-2088.**

**This Patient Information has been approved by the
U.S. Food and Drug Administration**

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affiliated company.**

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Issued: July 2016

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Instructions for Use
Xiidra™ (ZYE-druh)
(lifitegrast ophthalmic solution) 5%
for topical ophthalmic use

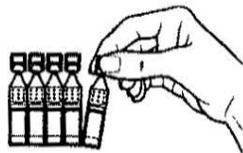
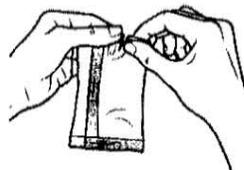
Read this Instructions for Use before you start using Xiidra™ and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment.

Important:

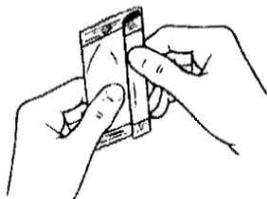
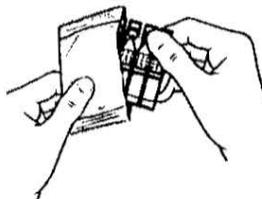
- Xiidra is for use in the eye.
- Wash your hands before each use to make sure you do not infect your eyes while using Xiidra.
- If you wear contact lenses, remove them before using Xiidra.
- Xiidra single use containers are packaged in a foil pouch. Do not remove from the foil pouch until you are ready to use Xiidra.
- Do not let the tip of the Xiidra single use container touch your eye or any other surfaces.
- Use 1 drop of Xiidra in each eye 2 times each day (1 drop in the morning and 1 drop in the evening, approximately 12 hours apart). Each single use container of Xiidra will give you enough medicine to treat both of your eyes, 1 time. There is some extra Xiidra in each single use container in case you miss getting a drop into your eye. After you have applied the drops, throw away the single-use container and any unused Xiidra. Do not save any unused Xiidra.

Follow Steps 1 to 9 each time you use Xiidra:

Step 1. Take a foil pouch out of the Xiidra box. Open the pouch and remove the strip of single use containers. Pull off 1 single use container from the strip.



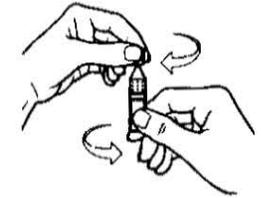
Step 2. Put the remaining strip of single use containers back in the pouch and fold the edge to close the pouch.



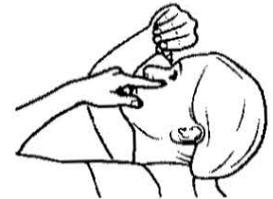
Step 3. Hold the Xiidra container upright. Make sure that the Xiidra solution is in the bottom part of the container.



Step 4. Open the Xiidra single use container by twisting off the tab. Make sure that the tip of the single use container does not touch anything, to avoid contamination.



Step 5. Tilt your head backwards. If you are not able to tilt your head, lie down.



Step 6. Gently pull your lower eyelid downwards and look up.

Step 7. Place the tip of the Xiidra single use container close to your eye, but be careful not to touch your eye with it.

Step 8. Gently squeeze the single use container and let 1 drop of Xiidra fall into the space between your lower eyelid and your eye. If a drop misses your eye, try again.

Step 9. Repeat steps 5-8 for your other eye. There is enough Xiidra in one single use container for both eyes.

Once you have applied a drop to both eyes, throw away the opened single use container with any remaining solution. If you use contact lenses, wait for at least 15 minutes before placing them back in your eyes.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421

For more information, go to www.Xiidra.com or call 1-800-828-2088.

This Instructions for Use has been approved by the U.S. Food and Drug Administration

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OPEN

Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-Year, Multicenter, Randomized, Placebo-Controlled Study

Eric D. Donnenfeld, MD, FAAO,* Paul M. Karpecki, OD, FAAO,† Parag A. Majmudar, MD,‡
Kelly K. Nichols, OD, MPH, PhD,§ Aparna Raychaudhuri, PhD,¶ Monica Roy, OD, MPH, FAAO,¶
and Charles P. Semba, MD¶

Purpose: To evaluate the 1-year safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease compared with placebo.

Methods: SONATA (Safety Of a 5.0% coNcentrATIOn of lifitegrAst ophthalmic solution) was a multicenter, randomized, prospective, double-masked, placebo-controlled phase 3 study (NCT01636206). Adults (≥ 18 years) with dry eye disease (Schirmer test score ≥ 1 and ≤ 10 mm; corneal staining score ≥ 2.0) were randomized 2:1 to lifitegrast ophthalmic solution 5.0% or placebo twice daily for 360 days. The primary objective was percentage and severity of treatment-emergent adverse events (TEAEs). Secondary objectives were ocular safety measures: corneal fluorescein staining, drop comfort, best-corrected visual acuity, slit-lamp biomicroscopy, and intraocular pressure over 7 visits. Exploratory objectives included concentration of lifitegrast in plasma.

Results: The safety population comprised 331 participants (220 lifitegrast; 111 placebo). There were no serious ocular TEAEs. Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular TEAE versus 34.2% in the placebo group; most TEAEs were mild to moderate in severity. Rates of discontinuation because of TEAEs were 12.3% (lifitegrast) versus 9.0% (placebo). The most common ($>5\%$) TEAEs occurring in either treatment group were instillation site irritation (burning), instillation site reaction, visual acuity reduced, dry eye, and dysgeusia (change in taste). Ocular safety parameters for lifitegrast were similar to placebo. The mean plasma lifitegrast concentration at 360

days ($n = 43$) was below the limit of detection. There was no indication of systemic toxicity or localized infectious complications secondary to chronic immunosuppression.

Conclusions: Lifitegrast ophthalmic solution 5.0% seemed safe and well tolerated in this study, with no unexpected adverse events.

Key Words: adverse drug reactions, dry eye disease, randomized controlled trial, safety

(*Cornea* 2016;35:741–748)

Lifitegrast is a small-molecule integrin antagonist that was developed as a treatment for dry eye disease (DED) by targeting an inflammatory pathway associated with DED. The efficacy and safety of lifitegrast ophthalmic solution 5.0%, when administered twice daily for 84 days in participants with DED, have been demonstrated in 3 randomized controlled studies. These are 1 phase 2 study¹ and 2 phase 3 studies (OPUS-1² and OPUS-2³). In OPUS-1, the coprimary sign endpoint of change from baseline to day 84 in inferior corneal staining score was significantly improved in patients with DED treated with lifitegrast compared with placebo. However, the coprimary symptom endpoint of change from baseline to day 84 on the visual-related function subscale was not met.² The results of the OPUS-2 study were recently published; they showed that in lifitegrast-treated patients with DED with a recent history of artificial tear use and at least moderate baseline symptomology (eye dryness score ≥ 40), there was a significant improvement in the coprimary symptom endpoint of eye dryness score compared with placebo. The coprimary sign endpoint of inferior corneal staining score was not met in OPUS-2.³ In the phase 2 study, and in OPUS-1 and OPUS-2, lifitegrast was generally well tolerated, and no serious ocular adverse events (AEs) were reported.

Lifitegrast is designed to target the inflammation associated with DED by blocking the binding of the integrin, lymphocyte function-associated antigen 1 (LFA-1), to its cognate ligand, intercellular adhesion molecule 1 (ICAM-1). Inflammation at the cellular level of the lacrimal gland and ocular surface plays a major role in DED and is associated with symptoms of eye dryness and discomfort.⁴ T-cell activation is critical in the inflammatory process and is influenced by LFA-1/ICAM-1 binding.⁵ The interaction of

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This study was funded by SARcode Bioscience (now a wholly owned subsidiary of Shire) and Shire.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

Reprints: Eric D. Donnenfeld, MD, 711 Stewart Avenue, Suite 160, Garden City, NY 11530 (e-mail: ericdonnenfeld@gmail.com).

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LFA-1 and ICAM-1 is important in T-cell adhesion, migration, proliferation, and cytokine release at sites of inflammation.⁶⁻⁹ Infiltration of T-cells in the conjunctiva¹⁰ and increased expression of ICAM-1 in lacrimal and conjunctival epithelial cells¹¹ have been demonstrated in patients with DED. Taken together, this evidence suggests that LFA-1/ICAM-1 binding is a logical pharmacological target in the treatment of DED. Lifitegrast has been shown in vitro to block the interaction between ICAM-1 and LFA-1, inhibiting T-cell activation and recruitment and reducing inflammation.¹²⁻¹⁴

The objective of the SONATA (Safety Of a 5.0% coNcentrATion of lifitegrAst ophthalmic solution) study was to examine the longer term safety profile of lifitegrast. To achieve this, we evaluated the 1-year safety of lifitegrast ophthalmic solution 5.0% in participants with DED compared with placebo.

MATERIALS AND METHODS

The SONATA study was a phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel-arm study conducted at 22 sites in the United States. The study was compliant with the Health Insurance Portability and Accountability Act, adhered to the tenets of the Declaration of Helsinki, and was registered at ClinicalTrials.gov (identifier, NCT01636206). Ethics committee approval was obtained before the study was started.

Participants

Eligible participants were adults aged ≥ 18 years who had a self-reported history of DED; best-corrected visual acuity (BCVA) of 0.7 logarithm of the minimum angle of resolution (logMAR) or better, corneal fluorescein staining score ≥ 2 (scale, 0-4) in ≥ 1 region (superior, inferior, or central), visual analog scale score ≥ 40 for either eye dryness or eye discomfort (scale, 0-100; 0 = no discomfort; 100 = maximal discomfort), use and/or desire to use artificial tears for DED in the past 6 months, and Schirmer test score (without anesthesia) ≥ 1 mm and ≤ 10 mm. All participants provided written informed consent. Individuals with secondary Sjögren 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 participation in the study: women who were pregnant or nursing an infant, those with contraindications or hypersensitivity to the investigational product, previous treatment with lifitegrast, use of any topical medication or antibiotics for the treatment of blepharitis or meibomian gland disease, ocular herpes or any other ocular infection within the last 30 days, blood donation or significant loss of blood within the last 56 days, ocular conditions or chronic illness that could affect study parameters, a disorder causing immunodeficiency, history of laser-assisted in situ keratomileusis or similar surgery within the last 12 months, history of neodymium:yttrium aluminum garnet laser posterior capsulotomy within the last 6 months, known history of alcohol/drug abuse that might interfere with

study participation, and those with DED secondary to scarring or destruction of conjunctival goblet cells. Prohibited medications during the study were topical ophthalmic nonsteroidal antiinflammatory agents, topical ophthalmic cyclosporine, and systemic steroids.

After day 14 (visit 3), the use of the following was allowed: artificial tears (≤ 4 times daily, as needed), contact lenses (daily disposable lenses only), topical ophthalmic/nasal antihistamines, mast cell stabilizers, and steroids (only loteprednol etabonate for ≤ 4 weeks at a time); information on their use was collected beginning at day 90 (visit 4).

Study Design

The investigational product was supplied as a sterile liquid solution containing lifitegrast at a concentration of 5.0% with ~ 0.2 mL in each dose vial. During the treatment period (days 0-360; Fig. 1), participants received twice-daily doses (in the morning and the evening just before bedtime) of either lifitegrast ophthalmic solution 5.0% or the vehicle as a placebo administered to the ocular surface as a single eye drop in both eyes. Compliance with treatment was assessed by reconciliation of used and unused investigational product vials collected from participants. Noncompliance was recorded as a protocol deviation if $>20\%$ of expected doses since last visit were missed or $>120\%$ of expected doses were taken.

Outcome Measures

The primary safety assessment was based on ocular and nonocular treatment-emergent adverse events (TEAEs). AEs were considered treatment emergent if they occurred after the first dose of the investigational product; definition of AEs included intercurrent illnesses or injuries that represented an exacerbation (increase in frequency, severity, or specificity) of preexisting conditions, for example, the worsening of dry eye. TEAEs were assessed by the investigator for severity (mild, moderate, severe) and relatedness (not related, possibly related, probably related) to the investigational product. The secondary study objective was to evaluate ocular safety measures (including corneal fluorescein staining, drop comfort, BCVA, slit-lamp biomicroscopy, and intraocular pressure) over 7 visits in 360 days.

Investigator verbatim terms were coded using the Preferred Terms of the Medical Dictionary for Regulatory Activities (version 14.1). For example, the verbatim terms of decreased visual acuity, worsening visual acuity, decreased vision, logMAR change ≥ 22 from visit 2, decreased vision (lost glasses), and decreased visual acuity of 30 letters from baseline were coded to visual acuity reduced. A number of verbatim terms involving ocular burning upon instillation of study drug were coded to the Preferred Term of instillation site irritation. Blurred/blurry vision, ocular discharge, or ocular pressure sensation upon instillation were coded to instillation site reaction. Verbatim terms for dysgeusia (change in taste) included but were not limited to taste perversion or bitter or metallic taste in the mouth.

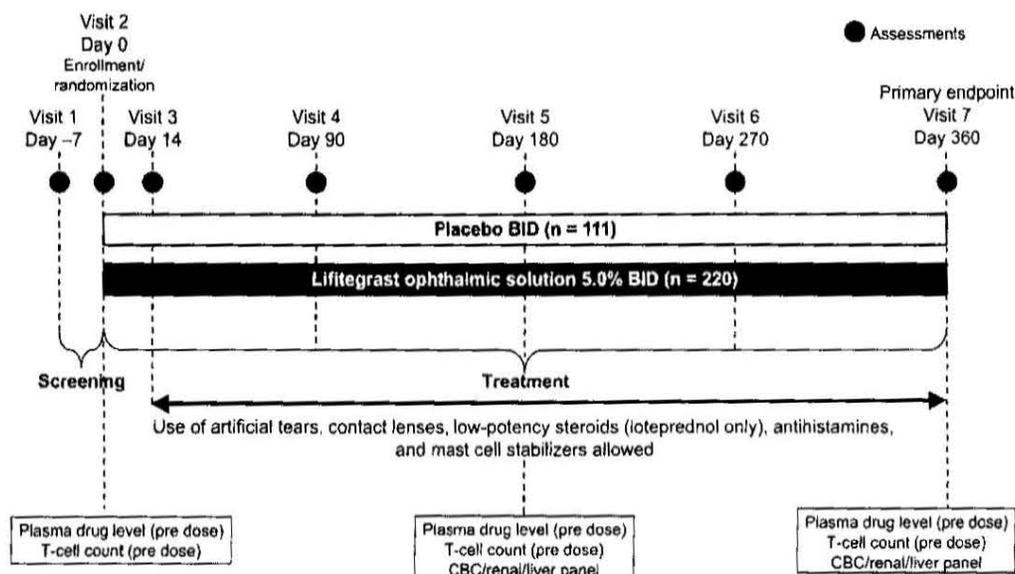


FIGURE 1. Study design schematic. BID, twice daily; CBC, complete blood count.

Exploratory objectives included the number and percentage of participants with TEAEs after using lifitegrast in conjunction with other topical eye drops, including artificial tears, steroids, mast cell stabilizers, and/or antihistamines, and after using lifitegrast in conjunction with contact lenses. Additional exploratory objectives included plasma lifitegrast concentration and whole-blood lymphocyte (CD3, CD4, and CD8) counts, which were collected from participants ($n = 75$) at selected study sites for each measure, and were obtained before administration of the investigational product at days 0 [visit 2 (baseline for lifitegrast levels and lymphocyte counts)], 180 (visit 5), and 360 (visit 7). Also in this category were clinical laboratory values (hematologic, renal, and liver panels) at days -7 [visit 1 (baseline for safety clinical laboratory tests)], 180 (visit 5), and 360 (visit 7). Participants were discontinued from the study if they requested to be withdrawn or at the discretion of the investigator and/or sponsor in accordance with their clinical judgment.

Randomization and Masking

An interactive web response system was used to randomly assign participants to receive lifitegrast or placebo based on a 2:1 ratio (lifitegrast:placebo). All study personnel were masked with regard to treatment assignments. No participants were unmasked during the study.

Statistical Methods

The safety population included all randomized participants who received ≥ 1 dose of the investigational product. Because this was a safety study, it was not powered for hypothesis testing to compare outcomes between the lifitegrast and placebo groups; statistical analyses were descriptive in nature. The study sample size was not based on statistical calculations or statistical assumptions, but on guidance provided by the US Food and Drug Administration and is

consistent with the International Conference on Harmonisation guidance on exposure for drugs intended for long-term treatment of nonlife-threatening conditions (International Conference on Harmonisation 1995). The method for assaying plasma samples for lifitegrast was linear over the range of 0.500 to 100 ng/mL, with a lower limit of quantification of 0.500 ng/mL. Samples below the lower limit of quantification were treated as 0 in the calculation of summary statistics.

RESULTS

Participants

The study was conducted between October 2012 and March 2014. Of the 504 participants screened, 332 participants were randomized (lifitegrast, $n = 221$; placebo, $n = 111$; Fig. 2). One participant in the lifitegrast group was erroneously randomized but never received treatment. As such, 331 participants were included in the safety population (lifitegrast, $n = 220$; placebo, $n = 111$).

Baseline characteristics were similar between treatment groups (Table 1). Participants' ages ranged from 21 to 89 years, with a mean (SD) age of 59.5 (12.68) years. The majority of participants were female and white. All participants 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 (41.1%), punctate keratitis (27.2%), nuclear cataract (19.0%), pinguecula (14.8%), and cataract surgery (13.9%). Within nonocular medical history, the most common ($>10\%$) occurrences were postmenopause (45.9%), hypertension (44.7%), hysterectomy (20.8%), gastroesophageal reflux disease (20.5%), hypercholesterolemia (18.1%), depression (15.4%), seasonal allergy (14.8%), increased blood glucose (14.5%), hypothyroidism (13.0%), drug hypersensitivity (13.9%), insomnia (13.6%), osteoarthritis (11.8%), and type 2 diabetes mellitus (11.5%).

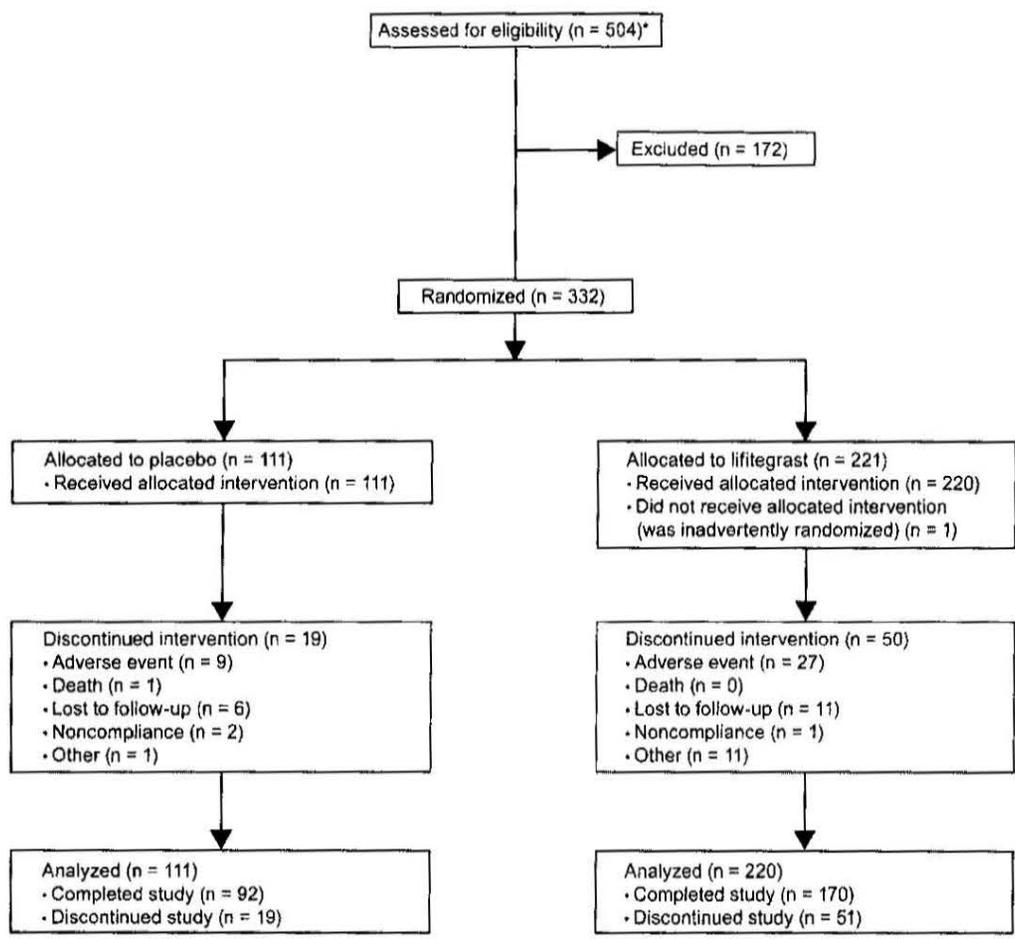


FIGURE 2. Participant flow. *Number may reflect multiple screenings for the same participant.

Overall, 38.1% of participants took an ocular concomitant medication with a start date on or after the first dose of investigational product, most commonly polyvinyl alcohol in artificial tear preparations (12.4%). Similar proportions of participants in each treatment group used contact lenses [lifitegrast, 2.6% (5/195) vs. placebo, 4.1% (4/98)], topical ophthalmic/nasal antihistamine [lifitegrast, 5.1% (10/195) vs.

placebo, 5.1% (5/98)], topical ophthalmic/nasal steroids [lifitegrast, 6.7% (13/195) vs. placebo, 5.1% (5/98)], and topical ophthalmic/nasal mast cell stabilizers [lifitegrast, 1.5% (3/195) vs. placebo, 1.0% (1/98)]. Data on concomitant use of medications or contact lenses were based on numbers too small to show trends in TEAE severity, relatedness, or seriousness. Based on investigational product vials returned, 81.1% of placebo-treated and 84.1% of lifitegrast-treated participants were compliant with study treatment.

TABLE 1. Participant Demographics

Characteristic	Placebo (n = 111)	Lifitegrast (n = 221)
Age, yr		
Mean (SD)	61.0 (13.18)	58.8 (12.39)
≥75, n (%)	15 (13.5)	19 (8.6)
Female, n (%)	85 (76.6)	165 (74.7)
Hispanic or Latino ethnicity, n (%)	17 (15.3)	33 (14.9)
Race, n (%)		
Asian	5 (4.5)	11 (5.0)
Black or African American	14 (12.6)	31 (14.0)
Native Hawaiian or other Pacific Islander	0	2 (0.9)
White	92 (82.9)	176 (79.6)
Other	0	1 (0.5)

Treatment-Emergent Adverse Events

A higher proportion of participants in the lifitegrast group experienced TEAEs compared with the placebo group (Table 2). TEAEs were categorized by the investigator as mild, moderate, or severe; in most participants with TEAEs, TEAEs were mild to moderate in severity (Table 2).

The most common (>5%) ocular TEAEs occurring in either treatment group were instillation site irritation (burning), instillation site reaction, visual acuity reduced, and dry eye; the most common (>5%) nonocular TEAE was dysgeusia (change in taste). Most TEAEs were mild to moderate in severity (Fig. 3; also see Table, Supplemental Digital Content 1, <http://links.lww.com/ICO/A396>). All

TABLE 2. Summary of Ocular and Nonocular TEAEs

TEAEs, n (%)	Placebo (n = 111)	Lifitegrast (n = 220)
Participants with ≥ 1 TEAE	59 (53.2)	160 (72.7)
Ocular TEAEs	38 (34.2)	118 (53.6)
Mild	27 (24.3)	85 (38.6)
Moderate	8 (7.2)	29 (13.2)
Severe	3 (2.7)	4 (1.8)
Nonocular TEAEs	40 (36.0)	104 (47.3)
Mild	20 (18.0)	55 (25.0)
Moderate	14 (12.6)	39 (17.7)
Severe	6 (5.4)	10 (4.5)
Participants with TEAEs considered possibly or probably drug related	27 (24.3)	104 (47.3)
Ocular TEAEs	23 (20.7)	88 (40.0)
Nonocular TEAEs	6 (5.4)	41 (18.6)
Participants prematurely withdrawn because of ≥ 1 TEAE	10 (9.0)	27 (12.3)
Ocular TEAEs	6 (5.4)	18 (8.2)
Nonocular TEAEs	4 (3.6)	9 (4.1)
Participants with serious TEAEs	6 (5.4)	9 (4.1)
Ocular TEAEs	0	0
Nonocular TEAEs	6 (5.4)	9 (4.1)
Participants with a TEAE resulting in death	1 (0.9)	0
Ocular TEAEs	0	0
Nonocular TEAEs	1 (0.9)	0

TEAE, treatment-emergent adverse event.

cases of instillation site irritation, instillation site reaction, and dysgeusia (change in taste) were considered possibly/probably related to the investigational product; a small

proportion of participants experienced visual acuity reduced (lifitegrast, 6.4%; placebo, 1.8%) and dry eye (lifitegrast, 1.8%; placebo, 3.6%) that were not considered related to the investigational product.

No serious ocular TEAEs occurred during the study, while 15 participants [lifitegrast, 4.1% (9/220) vs. placebo, 5.4% (6/111)] had serious nonocular TEAEs. One of these participants (in the placebo group) had a severe TEAE of sudden cardiac arrhythmia that resulted in death. All serious TEAEs were considered by the investigator to be not related to the investigational product, moderate to severe in severity, and resolved, except for arrhythmia (fatal outcome), spinal fracture (unknown outcome), and chronic obstructive pulmonary disease (resolved with sequelae). Chronic obstructive pulmonary disease was the only serious TEAE that occurred in >1 participant (lifitegrast, n = 0; placebo, n = 2).

Discontinuations Resulting From TEAEs

A total of 24 participants [lifitegrast, 8.2% (18/220) vs. placebo, 5.4% (6/111)] had ≥ 1 ocular TEAE and 13 participants had ≥ 1 nonocular TEAE [lifitegrast, 4.1% (9/220) vs. placebo, 3.6% (4/111)] that resulted in discontinuation. The most common TEAEs (experienced by >1 participant in either group) that resulted in discontinuation are presented in Table 3. In both treatment groups, most ocular TEAEs that led to discontinuation were considered mild to moderate in severity.

Secondary Safety Results

At each time point and visit, the mean drop comfort score (scale, 0–10; 0 = very comfortable, 10 = very

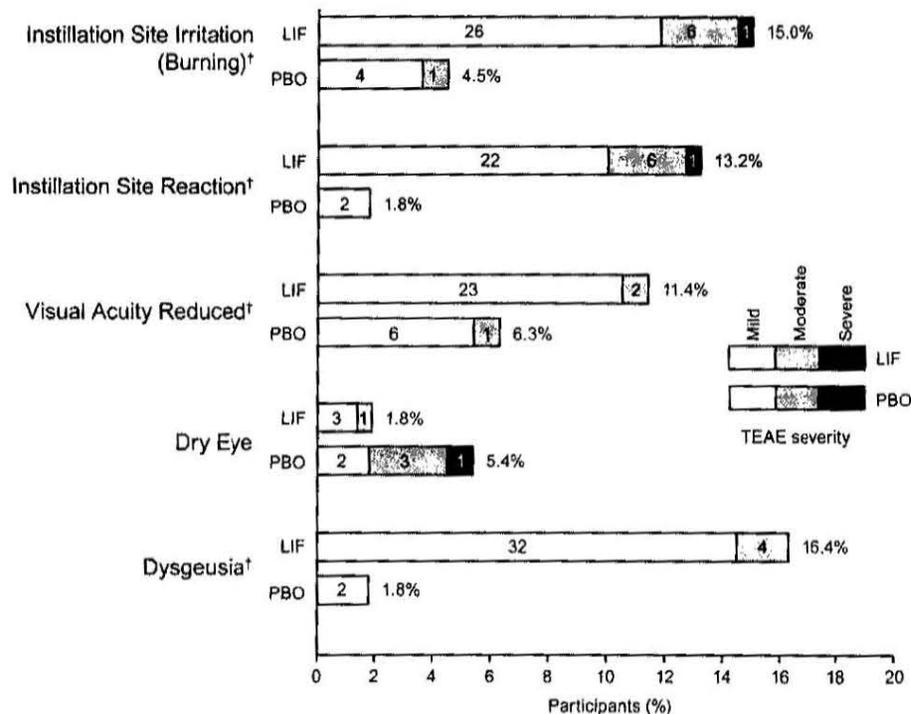


FIGURE 3. Incidence and severity of most frequent ($>5\%$) TEAEs*. Percentage value indicates the proportion of participants who experienced each type of TEAE. Values inside bars = numbers of participants. *TEAEs occurring in $>5\%$ of participants in either treatment group. [†]Verbatim terms coding to dysgeusia, instillation site irritation, instillation site reaction, and visual acuity reduced are given in the Materials and Methods section. LIF, lifitegrast; PBO, placebo; TEAE, treatment-emergent adverse event.

TABLE 3. Most Frequent TEAEs Leading to Discontinuations*

TEAEs, n (%)	Placebo (n = 111)	Lifitegrast (n = 220)
Ocular		
Lacrimation increased	1 (0.9)	3 (1.4)
Vision blurred	1 (0.9)	2 (0.9)
Visual acuity reduced†	0	3 (1.4)
Instillation site irritation† (burning)	2 (1.8)	2 (0.9)
Instillation site reaction†	0	4 (1.8)
Instillation site pain	1 (0.9)	2 (0.9)
Nonocular		
Dysgeusia†	0	4 (1.8)

*Findings are shown for TEAEs experienced by >1 participant in either group.

†Verbatim terms coding to dysgeusia, instillation site irritation, instillation site reaction, and visual acuity reduced are given in the Materials and Methods section. Overall rates of discontinuation are given in Table 2.

TEAE, treatment-emergent adverse event.

uncomfortable) of placebo-treated participants was numerically lower (more comfortable) than the drop comfort of lifitegrast-treated participants. However, in general, numerical improvement in comfort was observed within each visit (at each time point postinstillation) in the lifitegrast group. By 3 minutes postinstillation at each study visit, the lifitegrast group had mean drop comfort scores below 2 (Fig. 4).

The lifitegrast group had almost twice the frequency of participants with visual acuity reduced as the placebo group (11.4% vs. 6.3%, respectively). However, mean changes in logMAR BCVA from baseline to day 360 were minimal in both treatment groups [lifitegrast: no change (right eye, OD), +0.003 (left eye, OS); placebo: -0.026 (OD), -0.018 (OS); see Table, Supplemental Digital Content 2, <http://links.lww.com/ICO/A395>]. In addition, there were similar improvements in corneal fluorescein staining at each visit for all ocular regions examined (change from baseline to day 360), and no worsening in staining was observed in any region for

either treatment group (see Table, Supplemental Digital Content 2, <http://links.lww.com/ICO/A395>).

Similar mean intraocular pressures of the right and left eyes were measured between treatment groups at days -7, 180, and 360 (visits 1, 5, and 7; see Table, Supplemental Digital Content 2, <http://links.lww.com/ICO/A395>). In addition, generally, assessment of each eye on these days using slit-lamp biomicroscopy did not reveal any clinically significant abnormalities and there was no increased incidence of cataract formation in participants receiving lifitegrast [0.9% (2/220)] compared with those in the placebo group [0.9% (1/111)].

Exploratory Endpoint Results

Concomitant Artificial Tear Use

Overall, a lower proportion of participants in the lifitegrast group used artificial tears at any time after day 14 compared with the placebo group (Table 4). In addition, at each visit (days 90–360), the proportion of participants in the lifitegrast group who reported use of artificial tears since the last visit was numerically lower than that in the placebo group (Table 4).

Participants in both treatment groups who used artificial tears had higher rates of TEAEs compared with those not using artificial tears, respectively (ocular: lifitegrast, 67.2% vs. 45.0%; placebo, 44.2% vs. 25.5%; nonocular: lifitegrast, 60.9% vs. 42.7%; placebo, 44.2% vs. 32.7%). In general, a lower proportion of participants who used artificial tears had TEAEs that led to discontinuation compared with those who did not use artificial tears (ocular: lifitegrast, 3.1% vs. 3.1%; placebo, 0% vs. 1.8%; nonocular: lifitegrast, 0% vs. 2.3%; placebo, 0% vs. 3.6%).

Other Exploratory Endpoints

The mean changes in CD3, CD4, and CD8 counts from baseline to days 180 and 360 (visits 5 and 7) were minimal

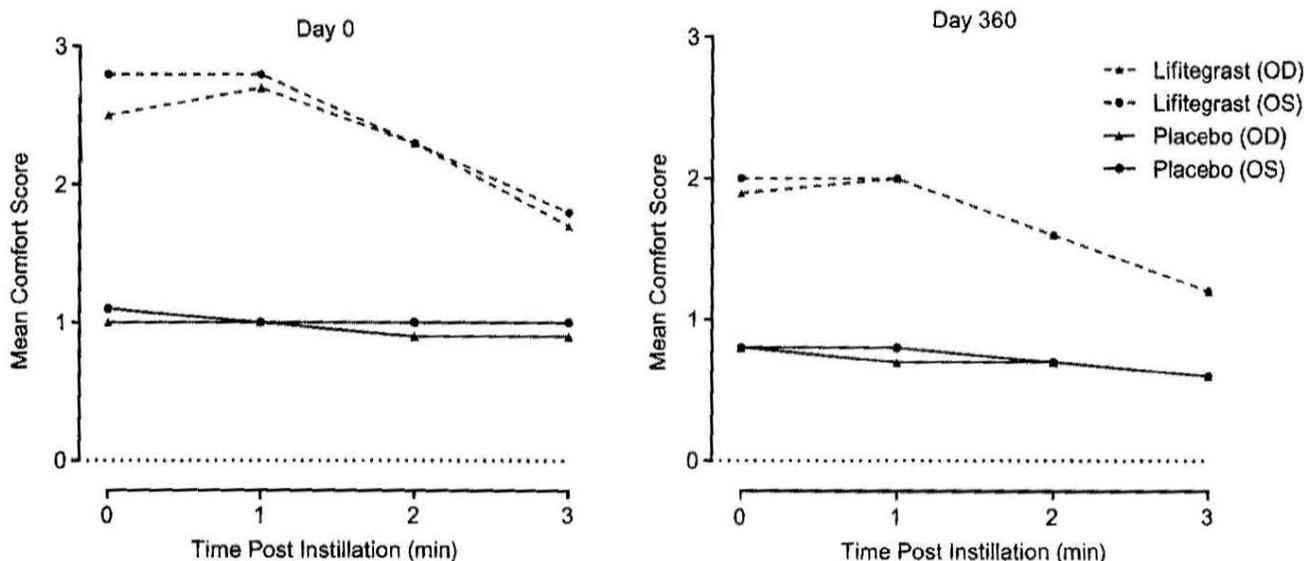


FIGURE 4. Drop comfort in a study of lifitegrast compared with placebo for dry eye disease. OD, right eye; OS, left eye.

TABLE 4. Artificial Tear Use in the Treatment Groups

Artificial Tear Use, n/n (%)	Placebo (n = 111)	Lifitegrast (n = 220)
No. of participants with any artificial tear use during the study	43/98 (43.9)	64/195 (32.8)
No. of participants with artificial tear use since last visit		
Day 90 (visit 4)	25/98 (25.5)	41/195 (21.0)
Day 180 (visit 5)	33/95 (34.7)	40/180 (22.2)
Day 270 (visit 6)	40/94 (42.6)	38/174 (21.8)
Day 360 (visit 7)	31/92 (33.7)	31/171 (18.1)

For days 90–360, the percentage of participants is based on the number of participants in the safety population with data at the visit. The question about artificial tear use (yes/no) was asked beginning at day 90 (visit 4).

and similar between the lifitegrast and placebo groups, with no trends to suggest chronic suppression of lymphocyte subset counts. No opportunistic infections or AEs to suggest chronic T-cell suppression were reported. In the hematologic, renal, and liver panels, the changes from baseline (day -7, visit 1) to days 180 and 360 (visits 5 and 7) were minimal and similar between treatment groups for all parameters.

The mean concentration of lifitegrast in plasma was below the lower limit of quantification (0.500 ng/mL) at days 0, 180, and 360. The mean plasma lifitegrast concentration at day 360 (n = 43) was 0.047 ng/mL.

DISCUSSION

SONATA is the first study to investigate the long-term safety of lifitegrast in the treatment of DED, and is one of a few multicenter, double-masked, placebo-controlled studies to investigate the safety of a drug treatment for DED over 12 months. In SONATA, no serious ocular TEAEs were reported, and the rate of discontinuations because of ≥ 1 TEAE was low in participants receiving lifitegrast (12.3%), albeit slightly higher than among those receiving placebo (9.0%). Approximately one-half of the participants who received lifitegrast reported ≥ 1 ocular TEAE across the 1-year study period; however, most TEAEs were mild to moderate in severity. Findings for the ocular safety measures of corneal fluorescein staining, drop comfort, BCVA, slit-lamp biomicroscopy, and intraocular pressure were comparable between the lifitegrast and placebo groups.

The safety profile observed in SONATA was consistent with that reported previously in shorter term studies of lifitegrast (84 days).¹⁻³ The most common ocular TEAEs attributed to lifitegrast were instillation site irritation, instillation site reaction, and visual acuity reduced, occurring in 15.0%, 13.2%, and 11.4% of participants, respectively. Importantly, discontinuation because of burning (coded under instillation site irritation) occurred in only 2 participants receiving lifitegrast, or 0.9% of the lifitegrast treatment group. Ocular TEAEs for lifitegrast seemed to be transient given that the most common ocular TEAEs were related to administration of the drug and that drop comfort improved within 3 minutes of instillation.

As with SONATA, the most commonly reported ocular TEAEs in earlier studies were administration site symptoms

(instillation site irritation, pain, and reaction) and visual acuity reduced, and the most common nonocular TEAE was dysgeusia (change in taste).¹⁻³ No new safety signals were identified in this 1-year study.

Visual acuity reduction was reported by participants in both lifitegrast and placebo groups. Visual acuity changes have been reported previously in studies of topical ophthalmic agents, including over-the-counter artificial tears.¹⁵ The tear film constitutes a critical component of the refractive properties along the visual axis,¹⁶ and instillation of eye drops may cause transient disturbances of the tear film, which may account for some of the visual acuity reduction in this study, although it should be noted that a slightly higher proportion of participants experienced visual acuity reduction in the lifitegrast group compared with the placebo group (11.4% vs. 6.3%, respectively).

The most commonly reported nonocular TEAE was dysgeusia (change in taste), which occurred in 16.4% of participants in the lifitegrast group and 1.8% of the placebo group. Clinically, this is a relatively common AE associated with instillation of some topical ophthalmic medications, because of normal tear drainage through the nasolacrimal duct into the nose and then into the oropharynx. The event is usually self-limited and short in duration. In the present study, discontinuations because of dysgeusia (change in taste) occurred in 4 participants receiving lifitegrast, or 1.8% of the lifitegrast treatment group. Fifteen participants (6 placebo, 9 lifitegrast) experienced serious nonocular TEAEs, which was consistent with medical complications in an older population.

There was no evidence of accumulation of lifitegrast in plasma over the course of the study, with most concentrations below the limit of detection on days 180 and 360. The very low plasma levels of lifitegrast in this study suggest that systemic side effects would not be expected after topical ophthalmic administration of lifitegrast. Indeed, there was no evidence of systemic toxicity or localized infectious complications secondary to chronic immunosuppression.

Artificial tear substitutes augment the tear film and are commonly used as a first-line therapy for DED. In the United States alone, artificial tears are used by ~7 to 10 million people.¹⁷ In this study, although TEAEs were more frequent in participants using artificial tears (in both treatment groups) than those who did not, concomitant use of artificial tears with lifitegrast did not result in a higher frequency of discontinuations because of TEAEs. Interestingly, a lower proportion of participants receiving lifitegrast used artificial tears compared with those receiving placebo, suggesting that the perceived need for artificial tears was lower in the lifitegrast group.

A limitation of this study was that patients with at least moderate baseline symptomology were enrolled, as inclusion criteria included corneal fluorescein staining score of ≥ 2 , eye dryness score ≥ 40 , and use and/or desire to use artificial tears in the past 6 months. Therefore, milder cases of DED would not have been studied. In addition, patients with a history of corneal surgery, such as laser-assisted in situ keratomileusis, within the past year also were excluded from this study, so the safety of lifitegrast in this group was not evaluated.

In conclusion, the use of twice-daily lifitegrast ophthalmic solution 5.0% for 360 days seemed safe and well tolerated, with

no unexpected TEAEs, and a safety profile that was similar to previous 12-week studies. The incidence of drug discontinuation was low, with 0.9% of participants withdrawing because of instillation site irritation (burning). In addition, there was no evidence of systemic toxicity or localized infectious complications secondary to chronic immunosuppression.

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