CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 30, 2015
Reviewer:	Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Acting Team Leader:	Naomi Redd, Pharm. D., DRISK
Acting Division Director:	Cynthia LaCivita, Pharm. D., DRISK
Subject:	Evaluation to determine whether a REMS is necessary to ensure that the benefits of lifitegrast 5% ophthalmic solution outweighs its risks
Drug Name:	XIIDRA (lifitegrast) Ophthalmic Solution 5%
Therapeutic Class:	Anti-inflammatory LFA-1 antagonist
Dosage, Form, Strength:	5% (50 mg/mL) ophthalmic solution, instill one drop of lifitegrast twice-a-day (b) (4) into each eye using a single (b) (4)
Office of New Drugs:	Division of Transplant and Ophthalmology Drug Products (DTOP)
Application Type/Number:	NDA 208-073, Original 00, received on February 25, 2015
Applicant:	Shire Development, LLC
PDUFA Deadline :	October 25, 2015
OSE RCM #:	2015-584 NME, PDUFA V Program, MASTER RECORD 2015-594 Risk Management Plan, NME, Priority Review

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for lifitegrast 5% ophthalmic solution, a new molecular entity (NME), small molecule drug proposed for the treatment of signs and symptoms of dry eye disease (DED) in adults. This original new drug application (NDA) 208-073 submission includes a brief proposed risk management plan (RMP) that does not include a REMS proposal.

The DRISK and the Division of Transplant and Ophthalmology Drug Products (DTOP) concurred that lifitegrast 5% ophthalmic solution does not require a REMS to ensure that the benefits outweigh its risks of eye irritation, eye pain, and dysgeusia (abnormal taste). The applicant's proposed RMP concludes that no clinically important risk was identified across the lifitegrast clinical development program. The majority of treatment emergent adverse events (TEAEs) were mild to moderate in severity and ocular in nature. The DTOP and the DRISK concluded that ophthalmology healthcare providers are informed on similar adverse reactions associated with use of ophthalmologic treatment exposure.

The prescription drug user fee act (PDUFA) goal date is October 25, 2015 for this Priority Review.

1 INTRODUCTION

The original NDA for lifitegrast ophthalmic solution was received by the DTOP on February 25, 2015. The lifitegrast clinical development program is under Investigational New Drug (IND) application 077-885 for SPD606 (lifitegrast) 5% Sterile Ophthalmic Solution and consists of 5 randomized, double-masked, placebo-controlled (PBO) clinical studies involving 1,896 patients: one study in healthy subjects and three multi-center, prospective, randomized, double-masked, PBO safety and efficacy studies.

These studies include one Phase (P) 2 study, 1118-KCS-100, and two P3 studies (1118-KCS-200 and 1118-DRY-300), currently referred to as OPUS-1 and OPUS-2, respectively, and one P3, long-term, multicenter, prospective, randomized, double-masked, PBO-controlled, parallel-arm safety study (1118-DRY-400) referred to as SONATA.

2 BACKGROUND

2.1 PRODUCT BACKGROUND

As explained by the applicant, lifitegrast selectively targets a T-cell surface adhesion molecule, is not considered an immunosuppressant, and claims to provide anti-inflammatory properties.[1] Lifitegrast is proposed as an anti-inflammatory small molecule antagonist of integrin lymphocyte function-associated antigen-1 LFA-1 (also known as CD11a/CD18 or αLβ2) (b) (4) for ophthalmic administration (as an eye drop). The applicant claims that lifitegrast binds to

[1] See NDA 208-073, XIIDRA (lifitegrast), Global Submit (GS), electronic (e) Common Technical Document (CTD) format, Module 2.5 Clinical Overview, 1. Product Development Rationale, p 8 of 59

LFA-1 and prevents interaction with its cognate ligand, ICAM-1 (known as CD54), inhibiting the leukocyte component of inflammation and immune activation including lymphocyte adhesion, infiltration, proliferation, and cytokine release. [1]

Lifitegrast is not an immunosuppressant. Its mechanism of action, based on non-clinical *in vitro* pharmacological studies, is to inhibit the protein-protein interaction between LFA-1 and ICAM-1.[2] Lifitegrast is proposed for the treatment of the signs and symptoms of dry eye disease in adults.

2.2 PROPOSED FORMULATION AND DOSAGE

The proposed to-be-marketed lifitegrast formulation and strength is as an ophthalmic solution 5% (50 mg/mL) administered as one drop twice a day in each eye (b) (4) using a single (b) (4) to be discarded immediately after use.

2.3 DISEASE CONDITION - DRY EYE DISEASE

Dry eye disease (DED) affects the tears and ocular surface which results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. [3] It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. [4]

The DED is associated with subjective symptoms as the most striking feature and, many times, the only information on which the diagnosis is based. [5] According to the National Eye Institute 2013 Report, due to the chronic nature of chronic DED, if left untreated, DED can progress to corneal scarring, ulcers, and ultimately vision loss.[6]

The prevalence in the United States (US) of DED as self-reported dry eye symptoms is estimated to be 7.8% of females aged 50 years and older [7] and 4.3% of males aged 50 years and older. [8] The US Census Bureau estimates for 2013, over 4.4 million females and over 2.1 million males over the age of 50 years are diagnosed with DED or have severe dry eye symptoms.

2.4 ARMAMENTARIUM OF THERAPY - TREATMENT FOR DRY EYES

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[2] NDA 208-073 Lifitegrast, GS, Section 22.1.3 Summary of Safety, page 18 of 111

[3] NDA 208-073, XIIDRA (lifitegrast), GS, Module 2.5 Clinical Overview, page 8 of 59

[4] Lemp Ma, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S, et al. (Definition and Classification Dry Eye Workshop subcommittee) 2007. The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye Workshop. *Ocul Surf*; 5(2): 75-92

[5] Versura P, Campos EC 2013 TearLab® Osmolarity System for diagnosing dry eye *Expert Rev Mol Diagn*; 13(2):119-29

[6] National Eye Institute 2013 Facts about Dry Eye *Dry Eye.* Viewed 04Sept2014, http://www nei.nih.gov/health/dryeye/factsaboutdryeye.pdf

[7] Schamburg DA, Dana R, Burning JE, Sullivan DA 2009. Prevalence of dry eye disease among US men: estiamtes form the Physicians' Health Studies. *Arch Ophthalmol*; 127(6):763-8

[8] Schamburg DA, Sullivan DA, Burning JE, Dana MR 2003. Prevalence of dry eye syndrome among US women *Am J Ophthalmol*; 136(2): 318-26

The approved and marketed treatments for dry eyes include artificial tears and punctal plugs [a tear duct plug (small medical device) that is inserted into the tear duct (puncta) of an eye to block the duct]. However, both artificial tears and punctal plugs only offer temporary relief and do not address the underlying disease process.

The only FDA-approved product indicated for treatment of DED is the cyclosporine, RESTASIS sponsored by Allegran, Inc. (NDA 050-790):

– RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, is a topical immune-modulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

  RESTASIS dosage and administration: instill one drop of RESTASIS ophthalmic emulsion, twice-a-day, in each eye approximately 12 hours apart.

  Labeling includes the following:

  - CONTRAINDICATIONS, *Section 4* cites "Restasis is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation."
  - WARNINGS AND PRECAUTIONS, *Section 5.1*, *Potential for Eye Injury and Contamination*, cites "to avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.
  - ADVERSE REACTIONS, *Section 6.1*, the most common adverse reaction following use of Restasis was ocular burning (17%). Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).
  - Postmarketing Experience, *Section 6.2*, reported reactions included hypersensivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

2.5 REGULATORY HISTORY

The regulatory history specific to NDA 208-073 for lifitegrast follows:

- **December 15, 2010**: IND 077-885, End of Phase 2 (EOP-2) Meeting in which the agency clarified to the sponsor that at least 300 patients need to complete at least 6 weeks of follow-up after initiation of lifitegrast treatment and at least 100 patients need to complete 12 months of follow-up after initiation of lifitegrast treatment prior to submission of the proposed NDA for lifitegrast.
- **October 1, 2012**: IND 077-885, EOP-2 Meeting in which the agency clarified to the sponsor that in order to demonstrate efficacy, a statistically significant difference between the study drug, lifitegrast, and the vehicle (PBO) should be shown for at least one pre-specified objective sign and subjective symptom of dry eye. Challenges with the clinical trial outcomes have been discussed since 2012:

- Study 1 (1118-KCS-100; P2) was not successful on its pre-specified *objective endpoint*, inferior corneal staining score (ICSS) from baseline to Day 84. There was no pre-specified subjective symptom endpoint in Study 1.
- Study 2 (1118-KCS-200; P3) was successful on its pre-specified *objective* co-primary endpoint, ICSS from baseline to Day 84, but was not successful on the pre-specified, co-primary *subjective* endpoint, visual-related function subscale of Ocular Surface Disease Index (VR-OSDI).

See the **Appendix**, to this review, **Table 1** for a summary of the primary and secondary endpoints employed across lifitegrast studies in support of this NDA.

The agency further clarified that at least one additional trial (P3), utilizing the to-be-marketed formulation, needs to confirm the objective endpoint of inferior corneal staining plus a pre-specified subjective symptom (preferably the same subjective endpoint as employed in an earlier trial) in a population of patients who use artificial tears. See cross-referenced entry dated **October 1, 2014.**

- **April 17, 2013**: Under IND 077-885, the clinical development of lifitegrast was originally submitted by SARcode Bioscience, Inc. (SARcode) and was later acquired by Shire on April 17, 2013.
- **May 15, 2014**: IND 077-885, Pre-NDA Type B Meeting. Discussion focused on the primary and secondary *sign* and *symptom* measures in the three lifitegrast studies.

– The agency clarified that an objective sign, ICSS in Study 2, and a subjective symptom, eye dryness score in Study 3, demonstrated a statistically significant treatment group difference in the respective studies. The DTOP expects that each of these positive results would be replicated in at least another P3 trial to demonstrate robustness of results and support a claim of substantial evidence.

The agency was not prepared to state that each endpoint (a *symptom* and a *sign*) have been replicated in more than one study. However, the agency clarified to the sponsor that these data would be filable. The agency clarified that whether the lifitegrast 5% ophthalmic solution (NDA 208-073) would be approved with the current clinical data would be a review issue. Though the sponsor preferred to discuss the totality of efficacy data, the sponsor acknowledged the lack of replication in two trials on the co-primary efficacy endpoints (a *sign* and a *symptom*) is a concern.

The agency emphasized in past discussions (October 1, 2012) that Shire should consider at least one additional Phase 3 clinical trial (similar in design to OPUS-2) which focuses on replicating findings that are statistically significant.

- **October 1, 2014:** The applicant submitted the final protocol for a P3 clinical trial, SHP606-304 (OPUS-3), as a multi-center, randomized, double-masked, PBO-controlled, parallel-arm, 12-week study evaluating the safety and efficacy of lifitegrast ophthalmic solution. The applicant plans to enroll 700 patients in OPUS-3.
  - The primary efficacy endpoint is measured by the eye dryness score (mean change from baseline to Day 84).

- Key secondary endpoints are to evaluate efficacy as measured by eye dryness score (mean change from baseline to Day 42 and mean change from baseline to Day 14).
- Study treatment is lifitegrast 5% ophthalmic solution or PBO ophthalmic solution; single eye drop, twice-a-day.

- **February 25, 2015**: The applicant submitted the original NDA 208-073/Sequence 000, Xiidra (lifitegrast) proposed for the treatment of signs and symptoms of dry eye disease in adults. See **Table 2**, **Section 3**, in this review.
- **February 25, 2015**: Sequence 001, The Division of Medication Error Prevention and Analysis (DMEPA) accepted the proposed proprietary name, Xiidra, initially submitted by Shire on August 9, 2013 (under IND 077,885).
- **May 21, 2015**: The DTOP Mid-Cycle Meeting for lifitegrast was inconclusive on whether the totality of clinical data will be acceptable for approval of the proposed indication. This DRISK reviewer briefly summarized the applicant's RMP and communicated that, at this time, a REMS is not needed for lifitegrast based on the current clinical safety data.
- **June 4, 2015**: Mid-Cycle Communication Meeting with the applicant. The DTOP Deputy Division Director underscored the significant clinical review issues, mainly the applicant's failure to achieve statistical significance on primary efficacy endpoint/co-primary efficacy endpoints in the three key studies. The applicant emphasized the totality of clinical data, including a post hoc dose-response analysis, and updated the DTOP on the ongoing study SHP606-304 (P3, OPUS-3). The applicant was informed on the inspection of manufacturing facilities and outstanding Chemistry and Manufacturing Control (CMC) issues. At the conclusion of this meeting, the applicant acknowledged the clinical review issues in NDA 208-073.

2.2 Materials Reviewed

- February 25, 2015: Original NDA 208-073 Xiidra (lifitegrast) 5% Ophthalmic Solution proposed for the treatment of signs and symptoms of dry eye disease in adults. This NDA includes a RMP (Module 1.16 Risk Management Plan).
- May 21, 2015: NDA 208-073 Xiidra (lifitegrast) Mid-Cycle Review, Clinical Review comments per Rhea Lloyd, MD, Clinical Efficacy Reviewer, DTOP; Statistical Reviewer, Solomon Chefo, Ph.D., DTOP; Cross-Discipline Team Leader, William Boyd, MD, DTOP; and Wiley Chambers, M.D., Deputy Director, DTOP.
- May 29, 2015: Label and Labeling Review written by Sarah K. Vee, Pharm. D., Division of Medication Error Prevention and Analysis (DMEPA).
- June 3, 2015: NDA 208-073/Seq 004 Xiidra (lifitegrast), 120-Day Safety Update Report. June 4, 2015: Mid-Cycle Communication Meeting held with the applicant.
- June 4, 2015: Mid-Cycle Communication Meeting
- *July 25, 2015: Pending* Clinical Efficacy Review for Lifitegrast 5% Ophthalmic Solution written by Rhea Lloyd, M. D., DTOP

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The applicant is seeking approval for the treatment of dry eyes in adults based on the efficacy and safety of lifitegrast (LIF) ophthalmic solution (5%) derived from three clinical trials. Each study was 14 weeks in duration with 5 study visits divided into a 2-week, open-label, PBO run-in screening period followed by a 12-week treatment period.

- **Study 1118-KCS-100, P2,** a multicenter, randomized, prospective, double-masked, PBO-controlled, parallel-arm study conducted in the US with 230 DED patients (pts) randomized to LIF, 0.1, 1.0, or 5.0% or PBO. The pt population had mild to moderately symptoms at baseline and all 230 pts were included in the intent-to-treat (ITT) population. The majority of pts in both treatment groups completed this study (LIF: 96%; PBO: 96%)
- **Study 1118-KCS-200 (OPUS-1) P3**, is a multicenter, randomized, prospective, double-masked, PBO-controlled, parallel-arm, with 295 pts randomized to PBO and 293 pts randomized to LIF. The pt population had mild to moderate symptoms at baseline and all 588 pts were included in the ITT population. The majority of pts completed this study (LIF: 96%, PBO: 96%).
- **Study 1118-DRY-300 (OPUS-2) P3**, is a multicenter, randomized, prospective, double-masked, PBO-controlled, parallel-arm study conducted in the US. Pts had a history of artificial tear use and were stratified by inferior corneal staining score [ICSS] (≤ 1.5 or > 1.5) and eye dryness score [EDS] (< 60 or ≥ 60). The majority of pts completed this study (LIF: 90%, PBO: 97%).

One safety study was completed by the applicant in support of this NDA:

- **Study 1118-DRY-400 (SPD606-303; SONATA)** P3 is a multicenter, randomized, prospective, double-masked, PBO-controlled, parallel arm study to evaluate ocular *safety measures*.

Results of Clinical Efficacy

A summary of primary efficacy endpoints across the three studies is shown in **Table 2**. See the **Appendix**, to this review, **Table 1** with definitions of each primary and secondary efficacy endpoint employed across the three studies.

Table 2 Summary of Primary Efficacy Endpoints in P2, OPUS-1, and OPUS-2

	Phase 2	OPUS-1 (Phase 3)	OPUS-2 (Phase 3)
Primary Sign	ICSS [a]	ICSS [b]	ICSS [b]
Primary Symptom	None pre-specified	VR-OSDI score [b]	EDS [b]

[a] At Day 84
[b] Change from baseline to Day 84
EDS=eye dryness score, ICSS=inferior corneal staining score, VR-OSDI=visual-related function subscale of Ocular Surface Disease Index
Reference: NDA 208-073 Lifitegrast, GS, Section 2.7.3 Summary of Clinical Efficacy, Table 5, page 26 of 91

Brief summary of each primary efficacy endpoint result (and secondary endpoint result) follows:

- **Study 1118-KCS-100 (Phase 2)**

Primary Efficacy Endpoint - ICSS (sign)

Per the applicant, ICSS (sign): the 0.1, 1.0, and 5.0% LIF groups did not have statistically significant differences from the PBO group in ICSS at Day 84 (Week 12) using Dunnett's test from an analysis of covariance (ANCOVA) model[9] (p=0.9381, p=0.3585, and p=0.1375, respectively). The applicant and DTOP Clinical Reviewer concur that although none were statistically significant, the 5% LIF group had the largest improvement over PBO. In a post-hoc analysis, the DTOP concurs with the observation of a trend of increasing numerical improvements with increased LIF doses, a dose-response from baseline in ICSS.[10]

Secondary Efficacy Endpoint - Corneal Fluorescein Staining Score (sign)

The LIF dose groups had numerically smaller increases from baseline to Day 84 (+0.25, +0.10, and +0.05 for the 0.1, 1.0, and 5.0% LIF groups, respectively) than the PBO group (+0.40). The 1% and 5% LIF groups had nominally significant differences from PBO in the change from baseline to Day 84 for ICSS (nominal p=0.0433 and p=0.0209, respectively, from t-test).[11]

Secondary Efficacy Endpoint - Total Corneal Fluorescein Staining Score (sign)

Numerical dose-responses were observed in total corneal fluorescein staining scores. The 5% LIF group had a mean improvement from baseline to Day 84 in total corneal fluorescein staining score (-0.05), and the 0.1% LIF (+0.41), 1.0% lifitegrast (+0.18), and PBO groups (+ 0.35) had mean increases from baseline to Day 84 in total corneal fluorescein staining score.[12]

Secondary Efficacy Endpoint - Schirmer Tear Test (sign)

The 1% and 5% LIF groups had numerically greater mean improvements from baseline to Day 84 compared to PBO.[13]

Secondary Efficacy Endpoint - Conjunctival lissamine green staining score (sign)

Changes from baseline to Day 84 were similar for all treatment groups.

Secondary Efficacy Endpoint - Ocular Surface Disease Index (OSDI) (symptom)

The PBO treatment group had a numerically greater mean decrease (improvement) in total OSDI score from baseline to Days 14 and 84 (Weeks 2 and 12, respectively) as compared to the LIF treatment group.[14]

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[9] Dunnett's test is a multiple comparison procedure to compare each of a number of treatments with a single control. Dunnett's method is used in ANCOVA to create confidence intervals for differences between the mean of each factor level and the mean of a control group. ANCOVA model is used to test for differences between group means when we know that an extraneous continuous variable affects the continuous outcome variable.

[10] NDA 208-073 Lifitegrast, GS, Section 2.7.3 Summary of Clinical Efficacy, page 27 of 91, and see Table 6 on page 28 of 91

[11] NDA 208-073 Lifitegrast, GS, Section 2.7.3 Summary of Efficacy, page 29 of 91

[12] NDA 208-073 Lifitegrast, GS, Section 2.7.3 Summary of Efficacy, page 30 of 91

[13] NDA 208-073 Lifitegrast, GS, Section 2.7.3 Summary of Efficacy, page 30 of 91

- **Study 1118-KCS-200 (OPUS-1) Phase 3**

Co-Primary Efficacy Endpoint: ICSS (sign)

The 5% LIF treatment group had a statistically significant mean improvement in the ICSS from baseline to Day 84 (Week 12) (-0.07) as compared to the PBO group (+0.17; p=0.0007)

Co-Primary Efficacy Endpoint: VR-OSDI (symptom)

The 5% LIF group failed to achieve a statistically significant mean improvement in VR-OSDI score from baseline to Day 84 (Week 12) (-0.11) as compared to PBO treatment group (-0.12; p=0.7860).

Secondary Efficacy Endpoint – Schirmer Tear Test (sign)

The 5% LIF treatment group had numerically higher mean STT scores (indicating more tear production) compared to the PBO group at Days 14 and 84 (Weeks 2 and 12, respectively.

Secondary Efficacy Endpoint – Total OSDI (symptom)

The PBO group had a numerically greater mean decrease (improvement) in total OSDI score from baseline to Days 14 and 84 (Weeks 2 and 12, respectively) as compared to 5% LIF treatment group.

- **Study 1118-DRY-300 (OPUS-2) Phase 3**

Co-Primary Efficacy Endpoint - ICSS (sign)

The 5% LIF group failed to achieve a statistically significant mean improvement in ICSS from baseline to Day 84 (Week 12) (-0.73) as compared to the PBO group (-0.71; p=0.6186).

Co-Primary Efficacy Endpoint - Eye Dryness Score (EDS)

The 5% LIF group had a statistically significant mean improvement from baseline to ay 84 (Week 12) in EDS (-35.30) as compared to the PBO group (-22.75; p<0.0001). The applicant claims that EDS symptoms in patients treated with LIF compared to PBO was observed as early as Day-14. [15]

Secondary Efficacy Endpoint - EDS (VAS) (symptom)

The 5% LIF group had a numerically greater mean improvement in eye discomfort score from baseline to Day 84 (Week 12) (-26.46) compared to PBO (-16.73) (nominal significance p<0.0001).

Secondary Efficacy Endpoint - Ocular Discomfort Score (ODS) in Study Eye (symptom)

The 5% LIF group had a numerically greater mean improvement in ODS from baseline to Day 84 Week 12) (-0.91) compared to the PBO group (-0.57) nominal significance p=0.0005**).**

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[14] NDA 208-703 Lifitegrast, GS, Section 2.7.3 Summary of Efficacy, page 33 of 91

[15] NDA 208-073 Lifitegrast, GS, Section 2.7.3 Summary of Efficacy, page 38 of 91

These efficacy results show a paradoxical relationship in the *sign* and *symptom* variables reported in OPUS-1 and OPUS-2. In OPUS-1, there appears to be a drug response in reducing corneal staining but no detection of a drug response in improving symptoms. In patients with a history of artificial tear use in OPUS-1 and OPUS-2, there appears to be a drug response in symptoms but the ability to detect a drug response in reducing corneal staining was not demonstrated. The Clinical Reviewer, CDTL, and Statistics Reviewer concur with these outcomes.

The Clinical Reviewer, the Cross Discipline Team Leader (CTDL), and Statistics Reviewer concur with the above efficacy summaries. See each discipline review in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) under NDA 208-073 for additional details.

Study Population and Demographics

A total of 1,536 patients with DED were enrolled in the three efficacy studies and showed demographic characteristics consistent with a DED population of predominately Caucasian, older females (mean age 60 years). The proportion of pts with a history of artificial tear use was approximately 47% and 44% in the P2 study and OPUS-1, respectively, and 100% in OPUS-2.

For disease severity signs (measured by ICSS) at baseline, OPUS-2 had the highest objective disease severity, followed by OPUS-1, and P2. For symptoms [measured by eye dryness score (EDS)], OPUS-2 had the highest symptoms severity at baseline.

Patient Disposition

Overall retention across the three studies was approximately 93%. In OPUS-2, there was a higher rate of withdrawal secondary to adverse events (AEs) in the study treatment group, LIF (7.3%) compared to PBO (0.8%). In the OPUS-2, the most common treatment emergent adverse events (TEAEs) that led to treatment discontinuation were: instillation site irritation (5 patients), eye irritation (4 patients), and blepharitis (3 patients). See the Clinical Efficacy Review by Rhea Lloyd, M. D. for details on these TEAEs reported in the pt disposition as apply to the efficacy analyses.

3.1 CLINICAL SAFETY

Clinical data from four studies in patients with DED comprise the integrated evaluation of safety:

- 1, Phase 2, double-masked, PBO-controlled, 12 Week, efficacy and safety study
- 2, Phase 3, double-masked, PBO-controlled, 12-week, efficacy and safety studies (OPUS-1 and OPUS-2)
- 1, Phase 3, double-masked, PBO-controlled, 1-year safety study (SONATA)

Extent of Exposure

In all the Dry Eye Studies pooled, 1,044 pts (All LIF) received at least 1 dose of LIF (0.1, 1.0, or 5.0%). The mean duration of exposure was 112.5 days for the PBO group and 125.0 days for the LIF group. The majority of patients (82.8%) had ≤ 3 months of treatment exposure to LIF. All dry eye studies, except SONATA, were 12-week studies.

There were 176 patients who were exposed to LIF for > 6 months and 170 patients who were exposed to LIF for ≥ 12 months (defined by the applicant as ≥ 355 days).[16]

In the 1-year safety study, SONATA, the mean duration of treatment was PBO 311.1 days; LIF 304.4 days). See applicant's Table 8 in NDA 208-703, Section 2.7.4 Summary of Clinical Safety, for additional details on mean treatment duration. As shown in **Table 3**, there were 1,867 pts (All Dry Eye Studies Pooled) in the total safety population.

Table 3 Summary of Treatment Exposure: All Dry Eye Studies Pooled (Safety)

	PBO N=823	All LIF N=1044	All Pts N=1867
Total duration of Rx exposure			
Mean (SD)	112.5 (89.84)	125.0 (107.09)	119.5 (100.2)
Pts w/duration of Rx exposure, n (%)			
0 to 3 months	707 (85.9)	838 (80.3)	1545 (82.8)
> 3 months	116 (14.1)	206 (19.7)	322 (17.2)
> 6 months	94 (11.4)	176 (16.9)	270 (14.5)
> 9 months	93 (11.3)	172 (16.5)	265 (14.2)
> 12 months	89 (10.8)	170 (16.3)	259 (13.9)

Ref: NDA 208-073 Lifitegrast, GS, Module 2.7.4 Summary of Safety, Table 5, page 21 of 111

3.1.1 Deaths

There were a total of 2 deaths (0.1%): 1 LIF treatment and 1 PBO group.

- A 72-year old male with DED who received LIF (1.0%), P2 study, with a medical history of hypercholesterolemia and hypertension. Cause of death is attributed to cardiac arrest after 53 days exposure to LIF, not causally attributed to LIF.
- A 68-year old female in the PBO group, SONATA safety study, with a medical history of hypertension, chronic obstructive pulmonary disease, and sleep apnea. Cause of death is attributed to arrhythmia after 54 days exposure to PBO.

See Clinical Review by Rhea Lloyd, M.D., for details on these two fatal cases.

3.1.2 Drop-Outs and/or Discontinuations

Across the All Dry Eye Studies, 6.3% of patients in the PBO group and 11.4% of patients in the LIF group were discontinued from the study. The most common reason for discontinuation in the LIF 5% group was an AE [PBO: 16 patients (1.9%); LIF 5%: 73 patients (7.0%)], the primary reason was "other" - disallowed medication, withdrawn consent, patient could no longer make required visits, lack of efficacy, personal issues, and insufficient days on study drug - (PBO: 2.3%; lifitegrast 2.4%).

[16] NDA 208-073 Lifitegrast, GS, Section 2.7.4 Summary of Clinical Safety, Table 5, page 20 of 111

The most common System Organ Class (SOC) that led to discontinuation was Eye Disorders. As cited earlier in **Section 3.1.1**, two patients died (LIF 5%: 1 patient; PBO: 1 patient). There was 1 patient (0.1%, PBO group) that discontinued from the study due to pregnancy.

Serious and Severe Adverse Events

In the 12-Week dry eye studies pooled, none of the TEAEs were ocular in nature and none of the serious non-ocular TEAEs occurred in more than 1 patient. Most of the serious TEAEs were moderate to severe in nature. All of the serious TEASEs were not causally attributed to LIF and resolved with the exception of bladder cancer (PBO group) with an unknown outcome according to the applicant. See Clinical Review by Rhea Lloyd, M. D.

– In the 12-Week dry eye studies, 1.5 % of patients in the PBO group and 5.6% of patients in the LIF 5% group had TEAEs.

  The most common severe ocular TEAEs were eye irritation (LIF 5%: 3 patients; PBO: 0) and instillation site irritation (LIF 5%: 3 patients; PBO: 0).

  A total of 1.5% of patients in the LIF 5% group and 1% of patients in the PBO group had severe non-ocular TEAEs. The most common (> 1% of patients) severe non-ocular TEAEs were vertigo (LIF 5%: 1 patient; PBO: 1 patient) and dysgeusia (LIF 5%: 3 patients; PBO: 0 patients).

– In the SONATA study, 5.4% of patients in the PBO group and 4.1% of patients in the LIF group (5%) had at least 1 serious TEAE.

  Chronic obstructive pulmonary disease was the only serious TEAE that occurred in more than 1 patient. All serious TEAEs were considered to be not related to LIF, moderate to severe in severity, and resolved, except for arrhythmia (fatal outcome), spinal fracture (unknown outcome), and chronic obstructive pulmonary disease (resolved without sequelae).

3.1.3 Common Adverse Events

There were 13.9% of patients in the PBO group and 42.4% of patients in the LIF 5% group reported with ocular TEAEs considered by the Clinical Reviewer to be related to LIF.

– The most common ocular adverse reactions were eye irritation (16%) and eye pain (15%) and the most common non-ocular adverse reaction was dysgeusia (15%). All of the ocular TEAEs were mild to moderate in severity, and all non-ocular TEAEs were mild in severity. The most common (> 5% of patients in either group) ocular TEAEs considered related to LIF were instillation site pain (LIF 5%: 15.5%; PBO: 3.2%), instillation site irritation (LIF 5%: 13.7%; PBO: 2.4%), and instillation site reaction (LIF 5%, 11.7%; PBO: 0.8%).

– The most common (> 5% of patients in either group) non-ocular TEAE considered related to LIF was dysgeusia (LIF 5%: 14.6%; PBO, 0.1%).

In the SONATA safety study, the LIF 5% group had 53.6% of patients with ocular TEAEs and in the PBO group, 34.2% of patients had ocular TEAEs.

- The most common (> 5%) ocular TEAEs in either group were: reduced visual acuity, dry eye, instillation site irritation, and instillation site reaction. A total of 7 patients had ocular TEAEs considered severe (LIF 5%: ocular hyperemia, foreign body sensation in eye, instillation site irritation and instillation site reaction; PBO: dry eye, cataract, and instillation site pain).
- The most common (>5%) non-ocular TEAE was dysgeusia. The LIF 5% group had a higher frequency of patients with dysgeusia [36 patients (16.4%) compared to 2 patients (1.8%) in the PBO group]. A total of 16 patients had non-ocular TEAEs considered severe (LIF 5%: neuropathy peripheral, upper respiratory tract infection, osteoarthritis, pulmonary fibrosis, hip fracture, wrist fracture, dehydration, myocardial infarction, colonic polyp, menorrhagia, and cholelithiasis).

3.2 ADVERSE EVENTS OF SPECIAL INTEREST

Infections

As the mechanism of action for LIF is claimed to affect T-cell activation, an assessment of infections was included in the analysis of clinical safety data.[17] The frequency of ocular TEAEs in the Infections and Infestations SOC was low (≤ 1.1% in either treatment group) and similar between treatment groups.

- 2 patients treated with LIF 5% had serious TEAE infections: 1 patient (OPUS-1) had an infectious peritonitis, and 1 patient in the SONATA study had pneumonia and urinary tract infection.

Dysgeusia

Dysgeusia was reported more frequently in the LIF 5% group (13.1 to 16.4%) than in the PBO group (0 to 1.8%) in the All Dry Eye studies pool. Across all patients who experienced dysgeusia, most patients had mild to moderate dysgeusia. One patient (0.1%) and 4 patients (1.8%) in the LIF 5% group in the 12-Week Dry Eye Studies Pool and SONATA, respectively, were withdrawn from LIF due to a TEAE of dysgeusia. No patient had a serious TEAE of dysgeusia.

Blurred Vision

Blurred vision occurred more frequently in the LIF 5% group (2.8 to 4.1%) than in the PBO group (0.6 to 3.6%) in the All Dry Eye Studies Pool, Controlled Adverse Environment (CAE) Studies Pool, OPUS-2, 12-Week Dry Eye Studies Pool, and SONATA. In the 12-Week Dry Eye Studies Pool, 2 patients (LIF 5%) were withdrawn from LIF due to TEAE of blurred visions. In the SONATA study, 1 patient in the PBO group and 2 patients in the LIF 5% group were withdrawn from treatment due to blurred vision. No patient had a serious TEAE of blurred vision.

Eye Pain

Eye pain or site instillation site pain occurred more frequently in the LIF 5% group (4.5% to 30.2%) than in the PBO group (1.1 to 6.8%) in the All Dry Eye Studies Pool, CAE

[17] NDA 208-073 Xiidra, GS, Module 2.7.4, Summary of Safety, page 69 of 111

Studies Pool, OPUS-2, 12-Week Dry Eye Studies Pool, and SONATA. In the 12-Week Dry Eye Studies Pool 1 pt in the PBO group and 3 patients in the LIF 5% group were withdrawn from treatment due to TEAE of eye pain, and 6 patients in the LIF 5% group were withdrawn from treatment due to a TEAE of instillation site pain. In the SONATA study, 1 patient in the PBO group and 2 patients in the LIF 5% group were withdrawn from treatment due to a TEAE of instillation site pain. The instillation site pin resolved upon discontinuing lifitegrast. No patient had a serious TEAE of eye pain or instillation site pain.

Eye Irritation, Eye Pruritus, Foreign Body Sensation in the Eyes, and Increased Lacrimation

No patient was reported with a serious TEAE with LIF for eye irritation, eye pruritus, foreign body sensation in the eyes, and increased lacrimation. See the Clinical Safety Review by Rhea Lloyd, M. D. The applicant's proposed labeling does not include any CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS.

3.3 120-DAY SAFETY UPDATE REPORT

The 120-day safety update report (SUR) on LIF (received on June 3, 2015) reports on a small number of completed patients in ongoing blinded Study SHP606-304 (OPUS-3). As of the cut-off date of April 20, 2015, a total of 268 DED patients are randomized in a 1:1 ration to LIF 5% or PBO of which 264 patients have been treated with at least one dose of LIF. As of the 120-Day SUR, a total of 36 patients have completed OPUS-3.

The AEs reported were consistent with the known clinical safety data reported from the previous P3 studies (OPUS-1, OPUS-2 and SONATA). There were no new AEs reported in the 120-Day SUR. A total of 65 of 264 patients (24.6%) had at least 1 ocular or non-ocular TEAE and the majority of these TEAEs were mild. To-date, there are no serious TEAE and no deaths are reported in OPUS-3.

Four pts (1.5%) had TEAEs that led to discontinuation. Three of these four patients (1.1%) had ocular TEAEs leading to LIF discontinuation: 1 patient each with eye irritation, eye pain, and ocular discomfort. One patient (0.4%) discontinued treatment due to non-ocular TEAEs of dysgeusia, headache, and sinus headache. Each of these events was mild to moderate and reported to be causally attributed to LIF exposure.

The most common ocular TEAE reported in ≥ 5% of patients were eye irritation (20 pts; 7.6%) and ocular discomfort (16 pts; 6.1%). The most common non-ocular TEAE was dysgeusia (13 pts; 4.9%). One patient had severe ocular TEAE on study Day 43, this patient experienced one episode of pruritus in both eyes that resolved the same day. This patient completed the study without recurrence of pruritus.

See the Clinical Safety Review by Rhea Lloyd, M. D. for details on the 120-Day SUR.

4 DISCUSSION

Lifitegrast (LIF), a NME, is a LFA-1 antagonist that targets T-cell surface adhesion molecules and claims to provide anti-inflammatory properties inhibiting leukocytes in inflammation and immune activation including lymphocyte adhesion, infiltration, proliferation, and cytokine release. [1] Under NDA 208-073, lifitegrast failed to achieve

statistical significance on the co-primary efficacy endpoints in both Phase 3 studies (OPUS-1 and OPUS-2) and on the primary efficacy endpoint in the Phase 2 study. See **Section 3**, in this review, for brief summary on each primary and secondary endpoint result in the three studies.

The most important safety risks associated with use of lifitegrast 5% ophthalmic solution are eye irritation, eye pain, and dysgeusia (abnormal taste). Dysgeusia was reported more frequently with LIF (13% to 16%) compared to PBO (0 to 1.8%) in the All Dry Eye studies pool. Of pts who experienced dysgeusia, most patients had mild to moderate dysgeusia. There were no serious treatment emergent adverse events of dysgeusia. The adverse events of eye irritation, eye pruritus, foreign body sensation in the eyes, and increased lacrimation were not reported as serious events in the three efficacy and safety studies with LIF.

There were two deaths (0.1%) in the LIF clinical program: one fatality with 5% LIF and one fatality in the PBO group. The pt fatality with 5% LIF was causally attributed to cardiac arrest after 53 days exposure to LIF. The pt fatality in the PBO group was causally attributed to arrhythmia after 54 days exposure to PBO.

The applicant's proposed RMP focuses on routine pharmacovigilance and does not include a REMS proposal or non-REMS education materials. At this time, the reported safety profile of LIF demonstrated no pattern of adverse event consistent with systemic toxicities, localized or systemic infections, or immune-suppressant complications that needs a REMS program for risk management. The applicant concluded that healthcare providers are informed on similar common adverse reactions associated with use of ophthalmologic treatment exposure. Restasis (cyclosporine ophthalmic emulsion) 0.05%, the single FDA-approved product for the treatment of DED, is not required to have a REMS program for risk management and has labeling that does not include a Medication Guide. Restasis is most often used by ophthalmology prescribers and this is confirmed with the ophthalmologist Clinical Reviewer, Rhea Lloyd, M. D.

In the LIF Mid-cycle Communication Meeting (held on June 4, 2015), the DTOP clarified to the applicant that clinical trials supporting a dry eye treatment indication need to demonstrate superiority of LIF over PBO in a *clinical sign* and a clinical symptom of dry eye in two or more clinical trials. The applicant is currently conducting a 3rd P3 trial in pts with DED (OPUS-3).

At this time, the DTOP does not plan to provide the applicant with comments on the proposed labeling or request any postmarketing commitments (PMCs) or postmarketing requirement (PMRs) for NDA 208-073 Xiidra (lifitegrast) 5% Ophthalmic Solution. At this time, it appears that the regulatory action for NDA 208-073 Xiidra (lifitegrast) will be a complete response.

5 CONCLUSION

The DRISK and DTOP concur that the risks of eye irritation, eye pain and dysgeusia (abnormal taste) associated with use of lifitegrast ophthalmic solution 5% were mild to moderate in severity and no serious adverse events were causally attributed to lifitegrast. The DRISK and the DTOP concur that, if lifitegrast were to be approved, a REMS will not be necessary to manage the risks cited above. The DTOP should consult the DRISK if

additional safety information is identified that warrants re-evaluation of the risk management measures for lifitegrast ophthalmic solution 5%.

APPENDIX:

Table 1 - Primary & Secondary Sign /Symptom Efficacy Measures in Phase 2, OPUS-1 and OPUS-2

Study	Endpoint	Sign Measures	Symptom Measures
Phase 2	**Primary**	**ICSS (mean at Day 84/Wk 12)**	**None**
	Secondary	Corneal fluorescein staining score	OSDI score (total, symptom subscale, VR-OSDI, trigger subscale)
		Schrimer Tear Test (STT)	Ocular discomfort (ODS)
		Conjunctival lissamine green staining score	Visual analogue scale (VAS) by symptom
		Blink rate	5-symptom assessment
		Conjunctival redness score	
		Tear film break-up time	
		Ocular Protection Index	
OPUS-1	**Primary**	**ICSS (mean change from baseline to Day 84/Wk 12)**	**VR-OSDI (mean change from baseline to Day 84/Wk 12)**
	Secondary	STT (mean at Days 14 and 84)	Total OSDI (mean change from baseline to Days 14 and 84)
OPUS-2	**Primary**	**ICSS (mean change from baseline to Day 84/Wk 12)**	**Eye Dryness Score (EDS) [VAS; mean change from baseline to Day 84/Wk 12)**
	Secondary	Total corneal fluorescein staining scores (mean change from baseline to Day 84) Nasal conjunctival lissamine green staining score (mean change from baseline to Day 84)	EDS (VAS; mean change from baseline to Day 84) ODS (mean change from baseline to Day 84)

Reference: NDA 208-073, Global Submit, Section 2.7.3. Summary of Clinical Efficacy, Table 1, p 21/ 91

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/s/

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06/30/2015
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