CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208073Orig1s000

SUMMARY REVIEW

Deputy Division Director Review for NDA 208073

Date	June 17, 2016
From	Wiley A. Chambers, M.D.
NDA	208073
Applicant	Shire Development, LLC.
Date of Submission/Resubmission	February 25, 2015/ January 22, 2016
Name	Xiidra (lifitegrast ophthalmic solution) 5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of the signs and symptoms of dry eye disease
Recommendation:	Recommended for Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Medical Officer Review	Rhea Lloyd, MD
Statistical Review	Solomon Chefo, PhD
Pharmacology Toxicology Review	María I. Rivera, PhD
Clinical Pharmacology Review	Gerlie Gieser, PhD
MMPP/OPDP	Sharon W. Williams, MSN, BSN, RN/Meena Ramachandra, PharmD
OSI	Roy Blay, Ph.D.
CDTL Review	William Boyd, MD
OSE/DMEPA	Michelle Rutledge, PharmD
Pediatric and Maternal Health	Suchitra M. Balakrishnan, MD, PhD

Quality Review Team

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Drug Product	Shrikant Pagay	OPQ/ONDP/DNDPI/NDPBIII
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Environmental Assessment (EA)	James Laurenson	OPQ/ONDP

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Xiidra (lifitegrast ophthalmic solution) 5% is a topical ophthalmic drug product intended to treat the signs and symptoms of dry eye disease. Dry eye disease is a condition in which either the quality or quantity of natural tears are insufficient to provide a thin tear film over the cornea and conjunctiva for at least as long as the interval between one blink and the next. The condition occurs in both men and women, is frequently associated with increasing age and is most common in post-menopausal women. It rarely occurs in children. The cause is unknown.

There are no approved therapies for the treatment of the signs and symptoms of dry eye disease. There are drug products which meet the conditions described in the Over-the-counter monograph and are available for temporary relief of burning and irritation due to dryness of the eye. There is one approved product for increasing tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation.

Xiidra is not a cure for the condition. Clinical studies have shown that after 12 weeks of topical treatment with Xiidra, there can be an improvement in the signs and symptoms of dry eye disease. While a number of signs and symptoms of dry eye disease were evaluated in the clinical trials of Xiidra, efficacy was established in the submission by demonstrating an improvement in a symptom (visual analog scale measure of eye dryness) and a sign (inferior corneal staining). These two endpoints were evaluated in multiple clinical efficacy trials. Improvement in the symptom was demonstrated in multiple trials at multiple time points [Day 14 (2 studies), Day 42 (4 studies) and Day 84 (3 studies)]. Three trials demonstrated improvement in the inferior corneal staining on Day 84.

Approximately 1400 patients were exposed to the drug product with at least 170 being treated for at least one year. The most serious adverse reactions reported were application site reactions (irritation, redness, itching), dysgeusia and reduced visual acuity. These events were relatively short in duration. Additional adverse reactions (ocular itching, redness, tearing, or headaches) occurred in less than 5% of treated subjects and were relatively minor in severity and limited in duration. The potential adverse reactions are easily recognized and will be included in the labeling. Unexpected risks can be monitored through routine drug product surveillance. The usual postmarketing collection and reporting of adverse events is expected to be sufficient. No additional proposed risk management actions are recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dry eye disease is a condition in which either the quality or quantity of natural tears are insufficient to provide a thin tear film over the cornea and conjunctiva for at least as long as the interval between one blink and the next. The condition occurs in both men and women, is frequently associated with increasing age and is most common in post-menopausal women. It rarely occurs in children. The cause is unknown.	• The severity of dry eye disease depends on the duration of time that the cornea and/or conjunctiva is not covered by a tear film. Clear vision is dependent on having a thin tear film over the central cornea. Discomfort and/or pain will occur if the tear film is absent from the cornea and/or conjunctiva for a prolonged period of time. The cornea and/or conjunctiva is at higher risk of infection or other injury when not covered by a tear film, including sight threatening injury.
Current Treatment Options	• There are no approved therapies for the treatment of the signs and symptoms of dry eye disease. There are drug products which meet the conditions described in the Over-the-counter monograph which are available for temporary relief of burning and irritation due to dryness of the eye. There is one approved product for increasing tear production in patients whose tear production is presumed to be suppressed due to ocular nflammation.	• There is a significant unmet need for products to treat the signs and symptoms of dry eye disease.
Benefit	• Of the four vehicle controlled clinical trials, at least two trials demonstrated improvement in a symptom of dry eye disease at days 14 (2 studies), 42 (4 studies) and 84 (3 studies). Three trials demonstrated improvement in a sign of dry eye disease at Day 84.	• The Division expects that a product with efficacy for the treatment of signs and symptoms of dry eye disease will demonstrate improvement in both a sign and a symptom, although not necessarily both in the same trial. Efficacy has been demonstrated at Day 84 by improvement in a clinical sign in three adequate and well controlled studies and by improvement in a clinical symptom in three adequate and well controlled studies.

Risk	• Approximately 1400 patients have been exposed to the drug product with at least 170 been treated for at least one year. The most serious adverse reactions were application site reactions (irritation, redness, itching), dysgeusia and reduced visual acuity. These events were relatively short in duration. Additional adverse reactions (ocular itching, redness, tearing, or headaches) occurred in less than 5% of subjects treated and were relatively minor in severity and limited in duration.	• The database appears adequate to evaluate the safety of the drug product. Adverse events were relatively minor and limited in duration.
Risk Management	• The expected risks, application site reactions (irritation, redness, itching), dysgeusia and reduced visual acuity have been identified in the proposed labeling. Unexpected risks can be monitored through routine drug product surveillance.	• Adequate and well controlled studies support the safety of the drug product for the treatment of the signs and symptoms of dry eye disease. The usual postmarketing collection and reporting of adverse events is expected to be sufficient. No additional proposed risk management actions are recommended.

2. Introduction/Background

Shire Development, LLC., submitted a new drug application for the new molecular entity, lifitegrast ophthalmic solution, 5% for the treatment of the signs and symptoms of dry eye disease. Lifitegrast ophthalmic solution 5% is an antagonist of LFA-1 formulated as a buffered sterile eye drop without an antimicrobial preservative.

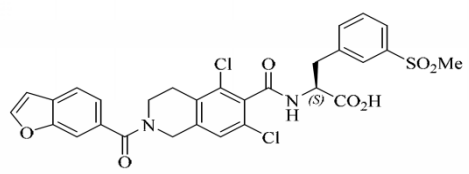
IND 77,885 for lifitegrast ophthalmic solution was submitted in July 2008. NDA 208073 was submitted on February 25, 2015. On October 16, 2015, a Complete Response (CR) letter for the original application was issued. In the CR letter, the Agency noted that there was a lack of substantial evidence to support efficacy in the NDA based on the clinical trials submitted at that point in time. On January 22, 2016, Shire responded to the CR with a submission which included an additional clinical trial.

3. Product Quality

USAN/INN: Lifitegrast

Chemical Name(s): (*S*)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid

Structure:



Molecular Formula: $C_{29}H_{24}Cl_2N_2O_7S$

Description and Composition of the Drug Substance:

Test	Acceptance Criteria	Analytical Procedure
Description	White to off-white powder	Visual Inspection
Identification – FTIR Spectrum	Conforms to reference spectrum	IR – USP <197>
Identification – HPLC Retention Time	Conforms to reference	HPLC
Assay by HPLC (weight %, [redacted])	95-105% (w/w)	HPLC
Purity by HPLC (area %)	≥96.0%	HPLC
Impurities by HPLC [redacted] (weight %) (weight %) (weight %) (weight %) (weight %) (weight %)	≤ [redacted] ≤ ≤ ≤ ≤ ≤	HPLC
[redacted] (weight %)	≤	UPLC
[redacted] (weight %)	≤	HPLC
Individual Unspecified Impurity (area%)	≤	HPLC
Total impurities*	≤	HPLC
Chiral Purity by HPLC (area %)	≥	HPLC
[redacted]	≤	[redacted]
Residual Solvents by GC [redacted]	NMT [redacted] NMT NMT NMT NMT	GC-FID
	NMT [redacted]	GC-FID
	NMT [redacted]	GC-FID
Residue on Ignition	NMT [redacted]	USP <281>
Microbial Limit Tests Total Aerobic Plate Count Total Yeast and Mold	 ≤ [redacted] CFU/g ≤ CFU/g	USP<61>
Bacterial Endotoxins	≤ [redacted] EU/mg	USP <85>
[redacted]	[redacted]	[redacted]
	NMT [redacted]	USP <231> Method II
	NMT [redacted]	[redacted]

* Total Impurities: Specified Impurities (weight %) + Individual Unspecified Impurities (area %)

Reviewer's Comment: *The controls are adequate from a clinical prospective.*

Drug Product Composition:

Ingredient	Amount	Function
Lifitegrast	5.0% w/v	Active
Sodium Chloride	(b) (4)	
Sodium Phosphate Dibasic, anhydrous		
Sodium Thiosulfate, pentahydrate		
Sodium Hydroxide, (b) (4)		
Hydrochloric Acid solution		
Water for injection		
(b) (4)		

Drug Product Container Closure:

Lifitegrast ophthalmic solution, 5% utilizes a (b) (4) foil laminate pouch as the primary packaging system. (b) (4) (b) (4) are not re-closeable and provide suitable drug product for a single instillation in each of two eyes. Additionally, a single card of 5 (b) (4) is sealed in a pre-printed aluminum foil laminate pouch. The (b) (4) is comprised entirely of low-density polyethylene (LDPE) (b) (4) (b) (4). Each (b) (4) is filled (b) (4) 0.20mL (b) (4) (b) (4) of solution.

Specification for Lifitegrast 5% Ophthalmic Solution

Test	Acceptance Criteria	Analytical Procedure
Appearance	Clear, colorless to slightly colored solution	Visual inspection
Color	(b) (4) *	USP <631>
pH	7.0-8.0	USP <791>
Osmolality	200-330 mOsm/kg	USP <785>
Lifitegrast Assay	(b) (4) of label claim	HPLC-UV Detector
Degradation Products		HPLC-UV Detector
Any unidentified degradation product	Not more than (b) (4)	HPLC-UV Detector
Total degradation products	Not more than	HPLC-UV Detector
Identification A: HPLC Retention Time	Major peak corresponds to Reference	HPLC-UV Detector
Identification B: UV Spectrum	Corresponds to Reference between 200-400 nm	HPLC-UV Diode Array
Minimum Fill Volume		USP<755>
Mean content	Not less than (b) (4)	
Content of any Single Container	Not less than	
(b) (4)	(b) (4) of Label Claim	HPLC-UV Detector
Particulate Matter (b) (4)	Not More Than (b) (4) Not More Than Not More Than	USP <789>
Sterility	No growth after (b) (4) days	USP <71>
Endotoxin	Not more than (b) (4) EU/mL	USP <85>

* The acceptance criterion is based upon analysis relative to (b) (4) reference solutions prepared as described in the current European Pharmacopeia, 2.2.2, "Degree of Coloration of Liquids."

Reviewer's Comment: *The controls are adequate from a clinical prospective.*

The Quality Review Team has completed their review of this application and have recommended that the application be approved from a quality prospective. Facility inspections have been completed and the facilities found to be in compliance with good manufacturing practices.

4. Nonclinical Pharmacology/Toxicology

Repeat-dose ocular toxicity studies of up to 39-week duration were conducted in dogs and rabbits at concentrations up to 5% administered topically 3x/day. Ocular findings in both species were limited to transient blinking and squinting, indicating mild ocular irritation. The squinting and blinking was not associated with any other abnormal ocular observations. The mild and transient nature of the findings observed does not present a major clinical concern.

Intravenous toxicity studies were conducted in dogs (7 and 4 weeks) and rats (13 weeks) at doses up to 30 mg/kg/day. No adverse findings were observed in the dog studies. Potential targets identified in the rat include the thymus (females only), urinary system, and male reproductive system. The NOAEL was 10 mg/kg. Based on AUC, the exposure margin for these findings is 400 to 700-fold.

In a fertility and embryofetal development toxicity study in rats, a fetal effect was apparent at the high dose (30 mg/kg), as reflected by an increase in mean preimplantation loss and increased incidence of several minor skeletal variations and malformations limited to 1 or 2 fetuses and litters. In males, there was a slight decrease in prostate (16%) and seminal vesicle (19%) weights at 30 mg/kg, but no effects were noted in fertility index. The NOAEL for male and female fertility was the high dose of 30 mg/kg; the NOAEL for embryofetal development was the mid dose of 10 mg/kg.

In a rabbit embryofetal development study, omphalocele was noted in a single fetus at the low dose of 3 mg/kg/day and the high dose of 30 mg/kg/day. In addition, there was an increased incidence of subclavian vein-supernumerary branch at the high dose, and bipartite ossification of the sternebrae at the mid dose and high dose. Omphalocele is an extremely rare malformation (i.e., noted in 1 fetus each in 2 litters from a total of 2237 litters in the historical database). As 2 litters had an affected fetus in the current study, it is difficult to definitely rule out a test article-related effect. The bipartite sternal ossification likely would not be adverse (expected to ossify as the animal continues growing). Based on the finding of omphalocele at the low dose and high dose, a fetal NOAEL was not identified in this study. Based on AUC, the exposure margin at the low dose of 3 mg/kg/day is 400-fold.

The original NDA submission included drug product and/or drug substance specifications which were not supported. The applicant has amended the application to tighten the specifications to levels which are either supported by clinical and/or nonclinical data, or are below the level of concern described in current Agency guidance documents.

There are no outstanding Pharmacology/Toxicology issues. The Pharmacology/Toxicology reviewer has recommended approval of the application.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology data in this NDA consists of plasma PK and tear fluid PK in healthy subjects enrolled in Phase 1 Study 001, sparse plasma PK and PD (lymphocyte counts) in a subset of dry eye disease patients enrolled in Phase 3 Study DRY-400 (SONATA), and *in vitro* data on lifitegrast metabolism in human hepatocytes, protein binding, and CYP2C9 inhibitory potential, as well as *in vitro* primary pharmacodynamic and cardiovascular safety pharmacology.

Human Pharmacokinetics and Pharmacodynamics (Clinical Studies)
In Phase 1 Study 001, the plasma and tear fluid pharmacokinetics (PK) of lifitegrast were investigated following topical ocular (single dose, twice daily and thrice daily) administration of various strengths of a *prototype* lifitegrast formulation.

In Phase 3 Study DRY-400 (SONATA), the plasma PK and the PD (effect on whole blood CD3, CD4, and CD8 lymphocyte counts) of lifitegrast were evaluated in a subset of 43 to 47 patients before and after twice daily dosing with the proposed commercial lifitegrast ophthalmic solution (5% w/v). At approximately 180 days and/or 360 days of repeated topical ocular dosing with lifitegrast 5%, 9 (~20%) of the patients included in the substudy had detectable (≥ 0.5 ng/mL) predose lifitegrast concentrations in the plasma. Of these 9 patients, 2 had predose concentrations that exceeded the EC50 (2.5 ng/mL) needed to inhibit T-cell adhesion *in vitro*, and an additional patient had treatment-emergent potentially clinically important (as per the sponsor) abnormalities in CD8 lymphocyte counts. The applicant stated that none of these 3 patients experienced systemic infections or immunosuppressive complications during the 12-month treatment period. Overall, these findings suggest that topical ocular (1 drop twice daily) administration of the proposed commercial lifitegrast 5% ophthalmic solution did not produce clinically significant lifitegrast exposures and inhibition of lymphocyte function in these dry eye disease patients.

Metabolism, Distribution, Drug Interaction, Pharmacodynamics (In Vitro Nonclinical Studies)
In addition to *in vitro* primary pharmacodynamic (e.g., on LFA-1 antagonism) and *in vitro* cardiovascular safety pharmacology (i.e., hERG channel inhibition) studies, the sponsor conducted preclinical investigations regarding the extent of hepatic metabolism, protein binding, and drug-drug interaction potential of lifitegrast, using *in vitro* human-derived systems. Overall, the clinical relevance of the *in vitro* findings is limited by the use of test concentrations substantially higher than that observed following topical ocular administration of lifitegrast 5% ophthalmic solution in healthy subjects and in dry eye disease patients.

There is no new Clinical Pharmacology information provided in the response to the CR letter. The Clinical Pharmacology Reviewer recommended approval of the application.

6. Clinical Microbiology

Not relevant. The product is not an antimicrobial drug product.

7. Clinical/Statistical - Efficacy

Four multicenter, randomized, double-masked, vehicle-controlled safety and efficacy trials were conducted in adult subjects with dry eye disease (Phase 2 Dry Eye Study, OPUS-1, OPUS-2, and OPUS-3) in addition to a yearlong safety trial (SONATA). The four trials were all similar in design.

The applicant's main efficacy analyses in each study compared a sign and/or a symptom in the treatment of patients with dry eye disease. The symptom was the mean change in Eye Dryness Score (EDS) as measured by a patient's mark on a visual analog scale. The sign was the mean change in Inferior Corneal Staining Score (ICSS). EDS and ICSS were measured endpoints in each of these trials, but the trials varied in the statistical analyses methods including the choice of the primary endpoint used to evaluate the treatment differences.

Table: Summary of the Primary Efficacy Endpoints and Applicant's Statistical Analysis Methods

	Phase 2	**OPUS-1**	**OPUS-2**	**OPUS-3**
Efficacy populations	ITT: included all randomized subjects	ITT: included all randomized subjects who received at least 1 dose of study drug.		
Primary Sign	ICSS at Day 84	Change from baseline in ICSS at Day 84	Change from baseline in ICSS at Day 84	Not Specified
Primary Symptom	Not specified	Change from baseline in VR-OSDI score at Day 84	Change from baseline in EDS at Day 84	Change from baseline in EDS at Day 84
Statistical methods for primary efficacy variable	ANCOVA Model: Response variable: ICSS at Day 84 Covariates: Treatment, study site, and baseline ICSS	2-sample t-test	Stratified 2-sample t-test: ANOVA model included treatment, strata, and the interaction between treatment and strata	Stratified 2-sample t-test: ANOVA model included treatment, strata, and the interaction between treatment and strata
Missing Data Approach	LOCF [1]: did not use baseline values for imputing missing post-baseline values	LOCF: used baseline values for imputing missing post-baseline values	LOCF [1]: did not use baseline values for imputing missing post-baseline values	LOCF: used baseline values for imputing missing post-baseline values
Stratification factors	N/A	Artificial tear use (yes/no) ICSS (≤1.0/>1.0)	ICSS (≤1.5 or >1.5) EDS (<60 or ≥60)	ICSS (≤1.5 or >1.5) EDS (<60 or ≥60)

ITT = intent-to-treat; LOCF=last observation carried forward; ICSS = inferior corneal staining score; VR-OSDI=visual related function subscale of Ocular Surface Disease Index; EDS=eye dryness score
[1]: **Seven** subjects in the Phase 2 study for both EDS and ICSS, and **five** subjects for EDS and **nine** subjects for ICSS in OPUS-3 study with only baseline values were excluded in the applicant efficacy analysis

For ease of review across study assessments, an analysis of covariance (ANCOVA) model is reported in this statistical review and below to analyze all the studies.

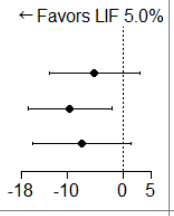
Efficacy Evidence for Clinical Symptom of DED

The summary of the mean change in EDS from baseline over time and the treatment differences (with 95% CI) based on the ANCOVA model are shown in Figure 1 below for each study.

Figure 1: Mean Change (SD) in Clinical Symptom (as measured in EDS) from Baseline over Time

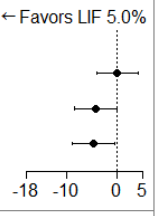
Phase 2

Visit	Placebo (N = 58)	LIF 5.0% (N = 58)	Difference[1] (95% CI)
Baseline	51.8 (23.55)	51.6 (24.69)	
Day 14	-3.9 (25.46)	-8.9 (21.72)	-5.1 (-13.1, 3.0)
Day 42	-7.9 (19.60)	-17.3 (24.96)	-9.4 (-17.0, -1.9)
Day 84	-7.2 (25.29)	-14.4 (25.36)	-7.3 (-16.1, 1.4)



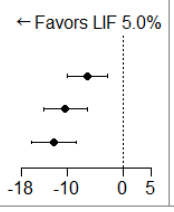
Phase 3: OPUS-1

Visit	Placebo (N = 294)	LIF 5.0% (N = 293)	Difference[1] (95% CI)
Baseline	41.6 (29.69)	40.2 (28.64)	
Day 14	-7.5 (29.01)	-6.7 (27.36)	0.1 (-3.9, 4.1)
Day 42	-9.1 (30.03)	-12.6 (30.71)	-4.2 (-8.5, 0.0)
Day 84	-11.2 (28.78)	-15.2 (31.48)	-4.7 (-8.9, -0.4)



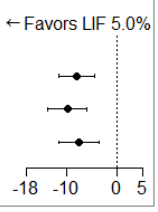
Phase 3: OPUS-2

Visit	Placebo (N = 360)	LIF 5.0% (N = 358)	Difference[1] (95% CI)
Baseline	69.2 (16.76)	69.7 (16.95)	
Day 14	-13.1 (24.04)	-19.7 (26.49)	-6.4 (-10.0, -2.8)
Day 42	-18.2 (26.51)	-28.3 (27.69)	-10.0 (-13.8, -6.1)
Day 84	-22.8 (28.60)	-35.3 (28.40)	-12.3 (-16.4, -8.3)



Phase 3: OPUS-3

Visit	Placebo (N = 356)	LIF 5.0% (N = 355)	Difference[1] (95% CI)
Baseline	69.0 (17.08)	68.3 (16.88)	
Day 14	-14.9 (22.35)	-22.7 (25.41)	-8.0 (-11.4, -4.5)
Day 42	-23.7 (25.98)	-33.0 (27.46)	-9.6 (-13.4, -5.8)
Day 84	-30.5 (28.03)	-37.7 (28.91)	-7.5 (-11.6, -3.5)



[1] Based on ANCOVA model that adjusted for baseline EDS in the Phase 2 study, and for baseline EDS and randomization stratification factors in the Phase 3 studies. All randomized and treated subjects were included in the analysis and missing data were imputed using last-available data (including baseline values if all post-baseline values were missing). In the Phase 2 study, one LIF 5.0% treated subject who did not have a baseline value was excluded from analysis.

In OPUS-2 and OPUS-3 studies, EDS was designated as a primary endpoint. Subjects treated with Xiidra demonstrated statistically superior improvement in the primary clinical symptom, EDS early on and continued improvement throughout the study compared to vehicle treated subjects. Although not designated as a primary endpoint in the either the Phase 2 study or in OPUS-1, there was a numerical difference in EDS favoring Xiidra in both studies at day 42 and day 84.

Taken as a whole, these trials support the treatment effect of Xiidra in improving a clinical symptom of DED, a change in the eye dryness score compared to vehicle.

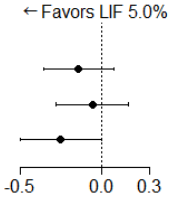
Efficacy Evidence for Clinical Sign of DED

The summary of the mean change in ICSS from baseline over time and the treatment differences (95% CI) based on the ANCOVA model are shown in Figure 2 below for each study.

Figure 2: Mean Change (SD) in Clinical Sign (as measured in ICSS) from Baseline over Time

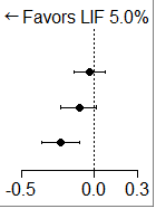
Phase 2

Visit	Placebo (N = 58)	LIF 5.0% (N = 58)	Difference[1] (95% CI)
Baseline	1.65 (0.513)	1.77 (0.515)	
Day 14	0.24 (0.709)	0.06 (0.522)	-0.14 (-0.36, 0.08)
Day 42	0.19 (0.694)	0.08 (0.591)	-0.05 (-0.28, 0.17)
Day 84	0.38 (0.785)	0.04 (0.745)	-0.25 (-0.50, -0.00)



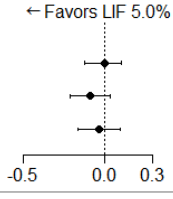
Phase 3: OPUS-1

Visit	Placebo (N = 294)	LIF 5.0% (N = 293)	Difference[1] (95% CI)
Baseline	1.81 (0.599)	1.84 (0.597)	
Day 14	0.08 (0.771)	0.04 (0.734)	-0.03 (-0.14, 0.08)
Day 42	-0.02 (0.893)	-0.14 (0.861)	-0.10 (-0.23, 0.02)
Day 84	0.17 (0.819)	-0.07 (0.868)	-0.23 (-0.36, -0.10)



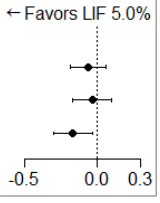
Phase 3: OPUS-2

Visit	Placebo (N = 360)	LIF 5.0% (N = 358)	Difference[1] (95% CI)
Baseline	2.40 (0.722)	2.39 (0.763)	
Day 14	-0.48 (0.798)	-0.48 (0.802)	-0.00 (-0.11, 0.11)
Day 42	-0.60 (0.899)	-0.69 (0.918)	-0.09 (-0.22, 0.04)
Day 84	-0.71 (0.943)	-0.73 (0.926)	-0.03 (-0.16, 0.10)



Phase 3: OPUS-3

Visit	Placebo (N = 356)	LIF 5.0% (N = 355)	Difference[1] (95% CI)
Baseline	2.46 (0.746)	2.46 (0.681)	
Day 14	-0.44 (0.775)	-0.49 (0.914)	-0.05 (-0.17, 0.07)
Day 42	-0.66 (0.927)	-0.69 (0.941)	-0.03 (-0.16, 0.10)
Day 84	-0.63 (0.911)	-0.80 (0.939)	-0.17 (-0.30, -0.03)



[1] Based on ANCOVA model that adjusted for baseline ICSS in the Phase 2 study, and for baseline ICSS and stratification factors in the Phase 3 studies. All randomized and treated subjects were included in the analysis and missing data were imputed using last-available data (including baseline values if all post-baseline values were missing). In OPUS-1 study, one Placebo treated subject who did not have a study eye designated was excluded from analysis.

In the Phase 2 trial, OPUS-1 and OPUS-2, ICCS was designated as a primary endpoint. Subjects treated with Xiidra demonstrated a statistically superior improvement in the primary clinical sign, ICSS at Day 84 in the Phase 2 trial and OPUS-1 compared to vehicle treated subjects. Although not designated as a primary endpoint in OPUS-3, there was a numerical difference in ICCS favoring Xiidra at day 84. In OPUS-2, both the Xiidra treatment group and the vehicle treatment group demonstrated sizable differences in ICCS, but there was no appreciable difference between the groups.

Taken as a whole, these trials, support the treatment effect of Xiidra in improving a clinical sign of DED, inferior corneal staining compared to vehicle.

8. Safety

The safety of lifitegrast 5% after 12 weeks of dosing is presented based on the 12-Week Dry Eye Studies Pool. The safety of lifitegrast after 1 year of dosing is presented based on the SONATA Study (1118-DRY-400) safety data. All subjects were treated twice a day in all studies.

Exposure

12-Week Dry Eye Studies Pool- Safety Population

	Vehicle N=712	All LIF N=710
Total duration of treatment exposure (days)		
Mean (SD)	81.8 (12.46)	79.0 (18.04)
Standard error	0.47	0.68
Median	85.0	85.0
Min, max	1, 132	1,95
Subjects with duration of treatment exposure, n (%) [b]		
0-3 months	692 (97.2)	696 (98.0)
> 3 months	20 (2.8)	14 (2.0)

Source: CSR, Module 2.7.4 Table 6: 12 Week Dry Eye Studies Pool (Phase 2, OPUS-1, and OPUS-2 Studies)

1 Year Study – Safety Population

	Vehicle N=111	5% LIF N=220
Duration of treatment exposure (days), mean (SD)	311.3 (114.29)	304.4 (112.50)
Duration of treatment exposure, n (%)		
> 0 months	111 (100.0)	220 (100.0)
> 3 months	96 (86.5)	194 (88.2)
> 6 months	94 (84.7)	177 (80.5)
> 9 months	93 (83.8)	173 (78.6)
≥ 12 months	89 (80.2)	170 (77.3)

Source: CSR, Module 2.7.4 Table 8

Deaths

There were two deaths reported during the clinical studies with lifitegrast.

Study	Cause of Death	Patient ID	Treatment group	Duration of Exposure	Other Medical Conditions
Phase 2 dry eye	Cardiac arrest	001-125 72/M	LIF 1%	53 days	Hypercholesterolemia, hypertension
SONATA	Arrhythmia	38-004 68/F	Vehicle	54 days	Hypertension, COPD, sleep apnea

Treatment Emergent Adverse Events Occurring in ≥ 1% in Vehicle or Lifitegrast 5% Treatment Groups in All Dry Eye Studies – Safety Population

Preferred Term	Vehicle N=1177 n (%)	5% LIF N=1287 n (%)
Ocular Treatment Emergent Adverse Reactions		
Subjects with at least 1 Ocular TEAE	250 (21.2)	594 (46.2)
Eye Disorders		
Visual acuity reduced	49 (4.2)	60 (4.7)
Vision blurred	12 (1.0)	38 (3.0)
Lacrimation increased	6 (0.5)	36 (2.8)
Eye irritation	10 (0.8)	33 (2.6)
Eye pain	8 (0.7)	25 (1.9)
Eye pruritus	13 (1.1)	22 (1.7)
Ocular hyperemia	6 (0.5)	20 (1.6)
Conjunctival hyperemia	11 (0.9)	16 (1.2)
Eye discharge	3 (0.3)	13 (1.0)
Dry eye	12 (1.0)	7 (0.5)
General Disorders and Administration Site Conditions		
Instillation site irritation	33 (2.8)	195 (15.2)
Instillation site reaction	27 (2.3)	158 (12.3)
Instillation site pain	25 (2.1)	126 (9.8)
Instillation site pruritus	9 (0.8)	42 (3.3)
Instillation site foreign body sensation	10 (0.8)	15 (1.2)
Non-ocular Treatment Emergent Adverse Reactions		
Subjects with at least 1 Non-Ocular TEAE	213 (18.1)	409 (31.8)
Infections and Infestations		
Nasopharyngitis	32 (2.7)	31 (2.4)
Sinusitis	12 (1.0)	14 (1.1)
Nervous system disorders		
Dysgeusia	4 (0.3)	186 (14.5)
Headache	8 (0.7)	29 (2.3)

Source: Module 2.7.4, ISS Tables 1.3.1.3 and 1.3.1.4
Note: TEAE are defined as AEs that occur after the start of randomized treatment or that worsen in severity compared to the pre-treatment state if the first onset of the AE is before the first treatment administration. Subjects are counted once per system organ class and once per preferred term; worst severity is used if a subject has multiple AEs of the same preferred term.

Safety Summary Statement

Adequate and well controlled studies support the safety of Xiidra (lifitegrast ophthalmic solution) 5% for the treatment of the signs and symptoms of dry eye disease. No serious ocular adverse reactions were reported in any study. There were two deaths reported in the clinical trials; both in patients with long standing cardiac disease. One was due to a cardiac arrest and the second, due to an arrhythmia in a patient treated with the vehicle. The most commonly reported ocular adverse reactions (10-25%) were instillation site complaints such as pain or discomfort upon instillation, irritation, itching or redness at the site of instillation. The next most frequent treatment emergent adverse reactions occurred in 5-15% of subjects were: 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.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

Because dry eye disease does not occur in sufficient numbers in the pediatric population, lifitegrast has not been studied in clinical studies with pediatric patients. This application was presented at the Pediatric Review Committee (PeRC) on May 14, 2015. PeRC concurred clinical studies in this population are impractical.

11. Other Relevant Regulatory Issues

REMS

The Division of Risk Management (DRISK) completed a Risk Evaluation and Mitigation Strategy (REMS) review on June 20, 2015. 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.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Xiidra, and granted conditional acceptance on April 29, 2015. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

FINANCIAL DISCLOSURE
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

OSI
A routine Office of Scientific Investigations (OSI) audit was completed. The studies appear to have been conducted adequately, and the data generated by each of each of these sites appear acceptable in support of the respective indication.

12. Labeling

The proposed labeling has discussed with the applicant. Revisions to the original labeling have been made and the package insert listed below is recommended.

13. Postmarketing

There are no recommended risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
06/17/2016

Deputy Division Director Review for NDA 208073

Date	October 5, 2015
From	Wiley A. Chambers, M.D.
NDA	208073
Applicant	Shire Development, LLC.
Date of Submission	February 25, 2015
Name	Xiidra (lifitegrast ophthalmic solution) 5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of the signs and symptoms of dry eye disease
Recommendation:	Not Recommended for Approval

1. Introduction/Background

Shire Development, LLC., submitted a new drug application for the new molecular entity, lifitegrast ophthalmic solution, 5% for the treatment of the signs and symptoms of dry eye disease. Lifitegrast ophthalmic solution 5% is an antagonist of LFA-1 formulated as a (b) (4) sterile eye drop without an antimicrobial preservative.

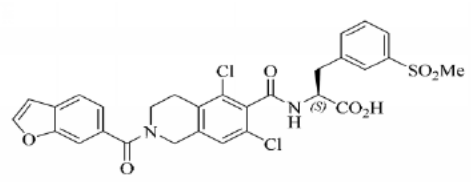
IND 77,885 for lifitegrast ophthalmic solution was submitted in July 2008. On May 15, 2014, a Pre-NDA meeting was held with the sponsor. The results of the lifitegrast clinical development program and proposed clinical data package for a NDA were discussed. Based on summary data, the Division communicated to the applicant that the studies may not support a finding of safety and efficacy of the product and recommended that the applicant consider conducting another trial based on the information learned to date.

2. Product Quality

USAN/INN: Lifitegrast

Chemical Name(s): (*S*)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid

Structure:



Molecular Formula: $C_{29}H_{24}Cl_2N_2O_7S$

Description and Composition of the Drug Substance:

Test	Acceptance Criteria	Analytical Procedure
Description	White to off-white powder	Visual Inspection
Identification – FTIR Spectrum	Conforms to reference spectrum	IR – USP <197>
Identification – HPLC Retention Time	Conforms to reference	HPLC
Assay by HPLC (weight %, (b) (4) (b) (4)	(b) (4) (w/w)	HPLC
Purity by HPLC (area %)	≥ (b) (4)	HPLC
Impurities by HPLC (b) (4) (weight %) (weight %) (weight %) (weight %) (weight %) (weight %)	≤ ≤ ≤ ≤ ≤ ≤	HPLC
(b) (4) (weight %)	≤	HPLC
Individual Unspecified Impurity (area%)	≤	HPLC
Total impurities*	≤	HPLC
Chiral Purity by HPLC (area %)	≥	HPLC
(b) (4)	≤	(b) (4)
Residual Solvents by GC (b) (4)	NMT (b) (4) NMT NMT NMT NMT	GC-FID
	NMT	GC-FID
	NMT	GC-FID
Residue on Ignition	NMT	USP <281>
Microbial Limit Tests Total Aerobic Plate Count Total Yeast and Mold	≤ (b) (4) CFU/g ≤ CFU/g	USP<61>
Bacterial Endotoxins	≤ (b) (4) EU/mg	USP <85>
(b) (4)	(b) (4)	(b) (4)
	NMT (b) (4)	USP <231> Method II
	NMT	(b) (4)

* Total Impurities: Specified Impurities (weight %) + Individual Unspecified Impurities (area %)
** Test to be performed on a minimum of 20 batches

As described in the Product Quality Review, it is premature to consider removing the tests for (b) (4). Additional manufacturing experience is needed prior to making this determination. The limit on (b) (4) has not been qualified. (b) (4) (b) (4), the limit should be decreased to the limit of detection (i.e., ≤ (b) (4)).

Drug Product Composition:

Ingredient	Amount	Function
Lifitegrast	5.0% w/v	Active
Sodium Chloride	(b) (4)	
Sodium Phosphate Dibasic, anhydrous		
Sodium Thiosulfate, pentahydrate		
Sodium Hydroxide, (b) (4)		
Hydrochloric Acid solution		
Water for injection		
(b) (4)		

Drug Product Container Closure:
Lifitegrast ophthalmic solution, 5% utilizes a (b) (4) foil laminate pouch as the primary packaging system. (b) (4) (b) (4) (b) (4) re-closeable and provide suitable drug product for a single instillation in each of two eyes. Additionally, a single card of 5 (b) (4) is sealed in a pre-printed aluminum foil laminate pouch. The (b) (4) is comprised entirely of low-density polyethylene (LDPE) (b) (4) (b) (4). Each (b) (4) is filled (b) (4) of (b) (4) 0.20mL (b) (4) of solution.

Specification for Lifitegrast 5% Ophthalmic Solution

Test	Acceptance Criteria	Analytical Procedure
Appearance	Clear, colorless to slightly colored solution	Visual inspection
Color	(b) (4) *	USP <631>
pH	(b) (4)	USP <791>
Osmolality	200-330 mOsm/kg	USP <785>
Lifitegrast Assay	(b) (4) of label claim	HPLC-UV Detector
Degradation Products		HPLC-UV Detector
Any unidentified degradation product	Not more than (b) (4)	HPLC-UV Detector
Total degradation products	Not more than	HPLC-UV Detector
Identification A: HPLC Retention Time	Major peak corresponds to Reference	HPLC-UV Detector
Identification B: UV Spectrum	Corresponds to Reference between 200-400 nm	HPLC-UV Diode Array
Minimum Fill Volume		USP<755>
Mean content	Not less than (b) (4)	
Content of any Single Container	Not less than	
(b) (4)	(b) (4) of Label Claim	HPLC-UV Detector
Particulate Matter (b) (4))	Not More Than (b) (4) Not More Than	USP <789>
Sterility	No growth after (b) (4) days	USP <71>
Endotoxin	Not more than (b) (4) EU/mL	USP <85>

* The acceptance criterion is based upon analysis relative to (b) (4) reference solutions prepared as described in the current European Pharmacopeia, 2.2.2, "Degree of Coloration of Liquids."

Facility Inspections: Acceptable.

The proposed specification is not acceptable.

1. As described in the Quality Reviews and Pharm/Tox Review, [redacted], there is no limit for [redacted] products. It is recommended that the specification [redacted] be revised [redacted] to Not more than 0.1% of the active ingredient. This would be consistent with other approved new drug products and control for potential expected and unexpected chemicals leaching from the carton, packaging and container materials.

2. The USP acceptance criterion for the Particulate Matter specification has changed to require a third criterion, Not More Than [redacted]. The proposed acceptance criterion for Particulate Matter should be consistent with the USP monograph.

In summary, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability, specifically,

1. There is not adequate safety information to support the drug substance specification limit [redacted]. Since no detectable levels [redacted] were present in the late-stage process batches tested to date (detection limit of [redacted] ppm), the acceptance limit should be revised to "less than [redacted] ppm."

2. The [redacted] is not acceptable. Removal of the test [redacted] may be requested in a supplemental application once adequate data is available.

3. In the leachable analysis in the stability study it is claimed that most of the impurities are degradents from the drug product and hence are not tracked in the leachables study. You should provide evidence that these impurities originate from the drug product. You should identify and qualify (i.e., provide safety data) the remaining unknown impurities that you identify as leachables.

4. One of the purposes of the specification is to identify potential issues with the manufacturing including unexpected issues. Changing the specification to all unidentified impurities and lowering the limit to the standard used for ophthalmic drug products (<0.1%) should minimize the chances that no harmful impurities (degradants, leachables or other) are included in the drug product.

5. The Comparability Protocol [redacted] both manufacturer and manufacturing process changes for both the drug substance and the drug product is not acceptable. The comparability protocol is not acceptable for either the proposed post-approval changes to the drug substance or the drug product. Additional data will need to be provided for a number of the proposed changes and changes to the

reporting categories will need to be made. It is recommended that the Comparability Protocol be revised or deleted from the new drug application.

In addition, the Quality Reviewers have asked that the following items, while not approvability issues, be included in the Complete Response Letter:

1. In the Amendment dated 16-Jun-2015, the method validation report for *Assay, Purity, Impurities, and Identification Test by HPLC (Test Method TM.2975)* was provided. The (b) (4) does not appear to give (b) (4) (b) (4) (b) (4). Thus, the HPLC method is not stability-indicating for all potential drug substance degradation pathways. It is recommended that the method be optimized (b) (4) for all potential degradation pathways or develop a new method that is stability-indicating.

2. The reconciliation table submitted in the amendment dated 6/10/2015 (table 1 of question 10) appears unclear, incomplete, and inaccurate. The following recommendations should be considered when the reconciliation table is revised and submitted.
   - The table should contain acceptance criteria for actual yield (minimum and maximum of the corresponding theoretical yield) for each phase of production as per CFR211.186(b)(7).
   - Provide definitions of the items listed in the first left column of the table, and indicate how they are calculated.
   - Waste/loss/rejects during manufacturing should be indicated for each step with proper explanation.
   - The actual yield for formulation (b) (4) should be the amount of solution available for filling plus that used for sampling, excluding any (b) (4).
   - Provide the actual and theoretical yield for packaging. The actual yield for this step should be (b) (4) (b) (4)
   - The reported (b) (4) is incorrect. It should be " (b) (4) (b) (4).

3. Nonclinical Pharmacology/Toxicology

Repeat-dose ocular toxicity studies of up to 39-week duration were conducted in dogs and rabbits at concentrations up to 5% administered topically 3x/day. Ocular findings in both species were limited to transient blinking and squinting, indicating mild ocular irritation. The squinting and blinking was not associated with any other abnormal ocular observations. The mild and transient nature of the findings observed does not present a major clinical concern.

Intravenous toxicity studies were conducted in dogs (7 and 4 weeks) and rats (13 weeks) at doses up to 30 mg/kg/day. No adverse findings were observed in the dog studies. Potential targets

identified in the rat include the thymus (females only), urinary system, and male reproductive system. The NOAEL was 10 mg/kg. Based on AUC, the exposure margin for these findings is 400 to 700-fold.

In a fertility and embryofetal development toxicity study in rats, a fetal effect was apparent at the high dose (30 mg/kg), as reflected by an increase in mean preimplantation loss and increased incidence of several minor skeletal variations and malformations limited to 1 or 2 fetuses and litters. In males, there was a slight decrease in prostate (16%) and seminal vesicle (19%) weights at 30 mg/kg, but no effects were noted in fertility index. The NOAEL for male and female fertility was the high dose of 30 mg/kg; the NOAEL for embryofetal development was the mid dose of 10 mg/kg.

In a rabbit embryofetal development study, omphalocele was noted in a single fetus at the low dose of 3 mg/kg/day and the high dose of 30 mg/kg/day. In addition, there was an increased incidence of subclavian vein-supernumerary branch at the high dose, and bipartite ossification of the sternebrae at the mid dose and high dose. Omphalocele is an extremely rare malformation (i.e., noted in 1 fetus each in 2 litters from a total of 2237 litters in the historical database). As 2 litters had an affected fetus in the current study, it is difficult to definitely rule out a test article-related effect. The bipartite sternal ossification likely would not be adverse (expected to ossify as the animal continues growing). Based on the finding of omphalocele at the low dose and high dose, a fetal NOAEL was not identified in this study. Based on AUC, the exposure margin at the low dose of 3 mg/kg/day is 400-fold.

With the exception of qualifying impurities, there were no additional non-clinical deficiencies.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology data in this NDA consists of plasma PK and tear fluid PK in healthy subjects enrolled in Phase 1 Study 001, sparse plasma PK and PD (lymphocyte counts) in a subset of dry eye disease patients enrolled in Phase 3 Study DRY-400 (SONATA), and *in vitro* data on lifitegrast metabolism in human hepatocytes, protein binding, and CYP2C9 inhibitory potential, as well as *in vitro* primary pharmacodynamic and cardiovascular safety pharmacology.

Human Pharmacokinetics and Pharmacodynamics (Clinical Studies)
In Phase 1 Study 001, the plasma and tear fluid pharmacokinetics (PK) of lifitegrast were investigated following topical ocular (single dose, twice daily and thrice daily) administration of various strengths of a *prototype* lifitegrast formulation.

In Phase 3 Study DRY-400 (SONATA), the plasma PK and the PD (effect on whole blood CD3, CD4, and CD8 lymphocyte counts) of lifitegrast were evaluated in a subset of 43 to 47 patients before and after twice daily dosing with the proposed commercial lifitegrast ophthalmic solution (5% w/v). At approximately 180 days and/or 360 days of repeated topical ocular dosing with lifitegrast 5%, 9 (~20%) of the patients included in the substudy had detectable (≥ 0.5 ng/mL) predose lifitegrast concentrations in the plasma. Of these 9 patients, 2 had predose concentrations that exceeded the EC50 (2.5 ng/mL) needed to inhibit T-cell adhesion *in vitro*, and an additional patient had treatment-emergent potentially clinically important (as per the sponsor) abnormalities

in CD8 lymphocyte counts. The applicant stated that none of these 3 patients experienced systemic infections or immunosuppressive complications during the 12-month treatment period. Overall, these findings suggest that topical ocular (1 drop twice daily) administration of the proposed commercial lifitegrast 5% ophthalmic solution did not produce clinically significant lifitegrast exposures and inhibition of lymphocyte function in these dry eye disease patients.

Metabolism, Distribution, Drug Interaction, Pharmacodynamics (In Vitro Nonclinical Studies)

In addition to *in vitro* primary pharmacodynamic (e.g., on LFA-1 antagonism) and *in vitro* cardiovascular safety pharmacology (i.e., hERG channel inhibition) studies, the sponsor conducted preclinical investigations regarding the extent of hepatic metabolism, protein binding, and drug-drug interaction potential of lifitegrast, using *in vitro* human-derived systems. Overall, the clinical relevance of the *in vitro* findings is limited by the use of test concentrations substantially higher than that observed following topical ocular administration of lifitegrast 5% ophthalmic solution in healthy subjects and in dry eye disease patients.

5. Sterility Assurance

The sterility and endotoxin limits were evaluated for the drug product. The manufacturing process was validated at (b) (4) for four consecutive validation batches.

Lifitegrast drug substance is packaged in one (b) (4) LDPE bag (b) (4). No product quality microbiology deficiencies were identified.

6. Clinical/Statistical - Efficacy

Three multicenter, randomized, double-masked, vehicle-controlled safety and efficacy studies were conducted in adult subjects with dry eye disease (DED). The Phase 2 Dry Eye Study (Study 1118-KCS-100) [100], OPUS-1 (Study 1118-KCS-200) [200] and OPUS-2 (Study 1118-DRY-300) [300] were all similar in design.

100: The primary efficacy endpoint was inferior corneal staining score (0-4 point Ora scale), of the designated study eye at Day 84.

200: The primary efficacy endpoints were the co-primary endpoints of mean change from baseline at Day 84, in inferior corneal fluorescein staining score and in the Visually Related-Ocular Surface Disease Index (VR-OSDI). The primary population was the ITT with LOCF.

300: The primary efficacy endpoints were the co-primary endpoints of mean change from baseline at Day 84, in inferior corneal fluorescein staining score and in eye dryness score (0-100 visual analogue scale, both eyes. The primary population was the ITT with LOCF.

Analysis of Primary Endpoint(s)

Study 100 – Inferior Corneal Staining Score at Day 84

	0.1% LIF N=57	1% LIF N=57	5% LIF N=58	Vehicle N=58
Mean (SD)	1.78 (0.473)	1.82 (0.508)	1.77 (0.515)	1.65 (0.513)
Day 84 (Week 12, Visit 5) N	57	55	54	55
Mean (SD)	2.03 (0.868)	1.92 (0.768)	1.83 (0.680)	2.05 (0.715)
Treatment effect (SE)	0.06 (0.138)	0.20 (0.139)	0.27 (0.140)	
95% confidence interval	(-0.26, 0.39)	(-0.13, 0.53)	(-0.06, 0.60)	
p-value	0.9381	0.3585	0.1375	

Analysis of covariance model with treatment, baseline, and site. P-value compared to vehicle from Dunnett's test.

None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score compared to vehicle based on Dunnett's test from the ANCOVA model. The results utilizing the Per Protocol population were similar. There were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses which suggested a dose-response.

Post Hoc Analysis – Corneal Fluorescein Staining Score (Ora Scale) for Artificial Tear Users

	0.1% LIF			1% LIF			5% LIF			Vehicle	
	n	Mean (SD)	p-value	n	Mean (SD)	p-value	n	Mean (SD)	p-value	n	Mean (SD)
Total corneal region											
Day 0 (Week 0, Visit 2, baseline)	22	3.98 (0.82)		27	4.54 (0.60)		31	4.34 (1.21)		29	4.47 (1.25)
Change from baseline to Day 14 (Week 2, Visit 3)	22	0.39 (1.57)	0.2837	26	0.12 (1.29)	0.5852	28	-0.04 (1.02)	0.8515	29	-0.10 (1.62)
Change from baseline to Day 42 (Week 6, Visit 4)	22	-0.18 (1.60)	0.8869	26	0.04 (1.59)	0.6990	28	0.27 (1.46)	0.3172	29	-0.12 (1.44)
Change from baseline to Day 84 (Week 12, Visit 5)	22	0.52 (1.89)	0.8367	26	0.37 (1.56)	0.5369	**28**	**-0.25 (1.42)**	**0.0280**	29	0.62 (1.49)
Inferior corneal region											
Day 0 (Week 0, Visit 2, baseline)	22	1.68 (0.52)		27	1.94 (0.42)		31	1.87 (0.53)		29	1.53 (0.53)
Change from baseline to Day 14 (Week 2, Visit 3)	22	0.14 (0.58)	0.5006	26	0.12 (0.61)	0.4137	28	0.05 (0.52)	0.2045	29	0.26 (0.68)
Change from baseline to Day 42 (Week 6, Visit 4)	22	0.07 (0.71)	0.4520	26	0.12 (0.52)	0.5342	28	0.11 (0.60)	0.5150	29	0.22 (0.74)
Change from baseline to Day 84 (Week 12, Visit 5)	***22***	***0.25 (0.91)***	***0.0453***	***26***	***0.15 (0.54)***	***0.0013***	***28***	***-0.07 (0.81)***	***0.0002***	***29***	***0.69 (0.62)***

This post-hoc analysis of artificial tear users demonstrated greater separation between lifitegrast 5% and vehicle.

Study 200- Inferior Corneal Staining Score at Day 84

	Vehicle N=294	**5% LIF N=293**
Baseline (Day 0) Mean (SD)	1.81 (0.599)	1.84 (0.597)
Day 84 (Week 12, Visit 5) Mean (SD)	1.98 (0.874)	1.77 (0.879)
Change from Baseline to Day 84 Mean (SD)	0.17 (0.819)	-0.07 (0.868)
Treatment effect (SE)		0.24 (0.070)
95% confidence interval		(0.10, 0.38)
p-value (t-test)		**0.0007**

ITT population for vehicle group is 295 subjects but 1 subject did not have a study eye designated due to a missed visit, therefore n=294 for vehicle group in analyses with evaluations of the study eye.
Note: Results presented in this table are from the study eye only.
Source: OPUS-1 CSR, Section 14, Table 3.1.1.1, Module 2.7.3 Table 7

In Study 200, the lifitegrast treatment group achieved a statistically significant mean decrease from baseline to Day 84 in one of the two co-primary endpoints, inferior corneal fluorescein staining score.

Study 200 Visual-related Function Ocular Surface Disease Index (VR-OSDI) Subscale Score

	Vehicle N=295	**5% LIF N=293**
Baseline mean (SD)	0.93 (0.958)	0.86 (0.931)
Day 84 mean (SD)	0.80 (0.838)	0.75 (0.861)
Change from Baseline to Day 84 Mean (SD)	-0.12 (0.762)	-0.11 (0.829)
Treatment effect (SE)		-0.02 (0.066)
95% confidence interval		(-0.15, 0.11)
p-value (t-test)		0.7860

Note: Results presented in this table are from the study eye only.
Source: Section 14, Table 3.1.1.2, Module 2.7.3, Table 8

The treatment group difference for the second co-primary efficacy endpoint, visual-related function ocular surface disease index subscale score, was not statistically significant.

Study 300 Inferior Corneal Staining Score

	Vehicle N=360	**5% LIF N=358**
Baseline (Day 0) mean (SD)	2.40 (0.72)	2.39 (0.76)
Day 84 mean (Week 12, Visit 5) (SD)	1.69 (1.01)	1.66 (1.04)
Change from Baseline to Day 84 Mean (SD)	-0.71 (0.94)	-0.73 (0.93)
Treatment effect (SE)		0.03 (0.067)
95% confidence interval		(-0.10, 0.17)
p-value (t-test)		0.619

ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. Note: Results presented in this table are from the study eye only.
Source: OPUS-2 CSR, Table 9, Section 14, Table 3.1.1.1, Module 2.7.3 Table 10.

Unlike Study 200 (or the subpopulation of Study 100) in Study 300, the lifitegrast treatment group did not achieve a statistically significant mean decrease from baseline to Day 84 in inferior corneal fluorescein staining score compared to the vehicle treatment group.

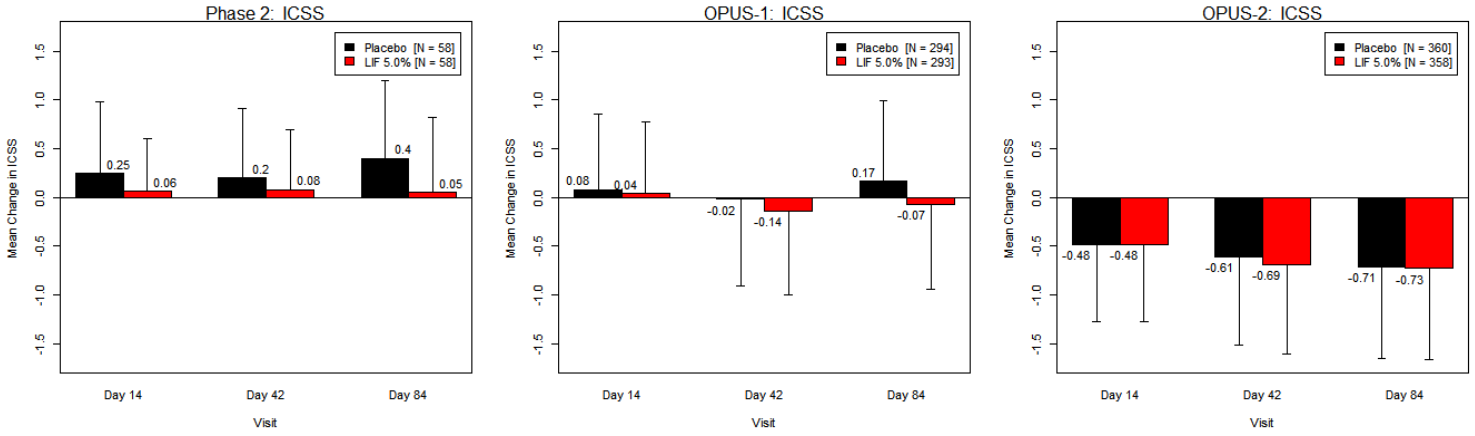
Study 300 Eye Dryness Score (Visual Analogue Scale)

	Vehicle N=360	**5% LIF N=358**
Baseline mean (SD)	69.22 (16.76)	69.68 (16.95)
Day 84 (Week 12, Visit 5) mean (SD)	46.47 (29.87)	34.39 (27.86)
Change from Baseline to Day 84 Mean (SD)	-22.75 (28.60)	-35.30 (28.40)
Treatment effect (SE)		12.613 (2.08)
95% confidence interval		(8.51. 16.70)
p-value (t-test)		**<0.001**

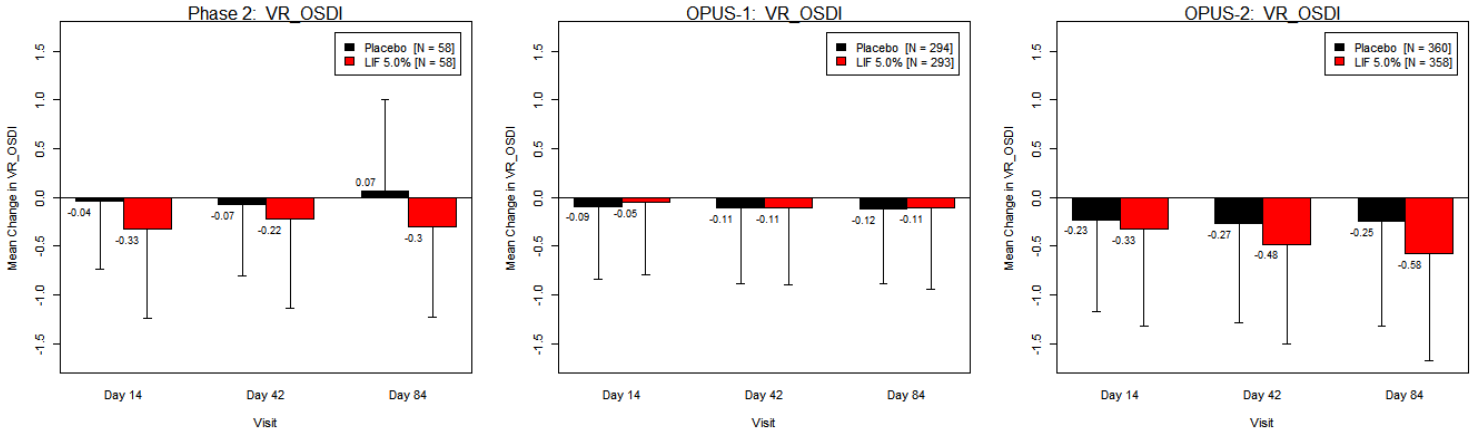
ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. Note: Results presented in this table are from the study eye only.
Source: Section 14, Table 3.1.1.2

The treatment group difference for the symptom co-primary efficacy endpoint, visual-related function ocular surface disease index subscale score was statistically significant in favor of the lifitegrast treatment group. This finding has not been replicated in any other trial of this product.

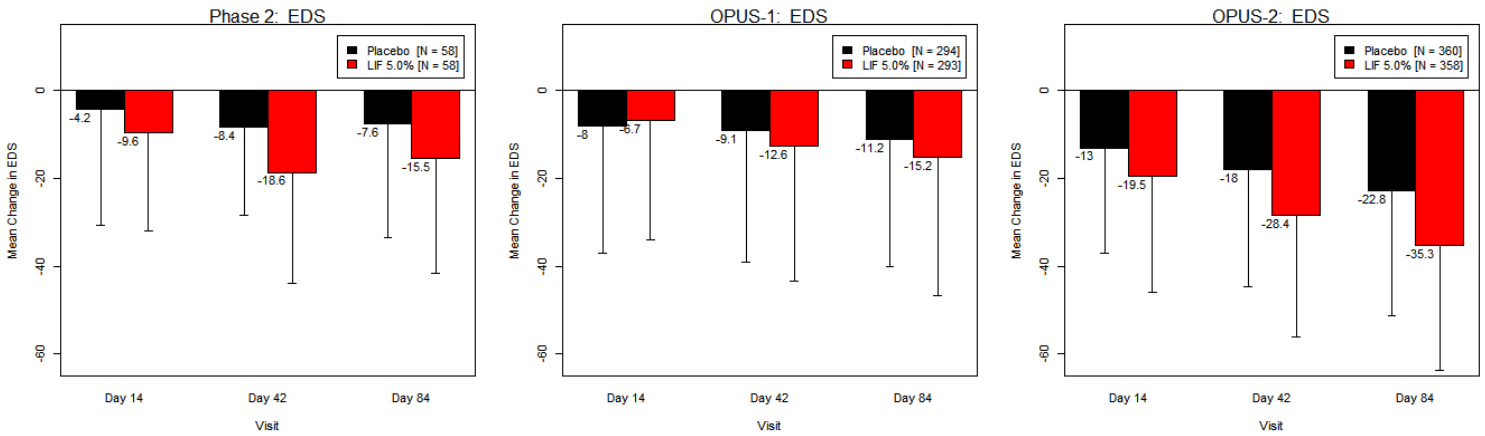
Mean Change in ICSS from Baseline at each Visit (Standard Deviation) **(ITT Population, LOCF)**



Mean Change in VR_OSDI from Baseline at each Visit (Standard Deviation) **(ITT Population, LOCF)**



Mean Change in Eye Dryness Score from Baseline at each Visit (Standard Deviation) **(ITT Population, LOCF)**



Summary Efficacy Statement

The application does not provide substantial evidence of efficacy for lifitegrast ophthalmic solution, 5%, in the treatment of dry eye disease because the trials fail to demonstrate consistency in their findings. Efficacy in predefined endpoints was repeatedly not demonstrated.

a) The Phase 2 Dry Eye study did not meet its primary efficacy endpoint, inferior corneal staining score at Day 84. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 84 compared to vehicle although there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.

b) The OPUS-1 study, which was designed based on post-hoc analyses of the Phase 2 Dry Eye study, did not meet its co-primary efficacy endpoints; change from baseline to Day 84 in inferior corneal staining score and visual related function Ocular Surface Disease Index subscale score. Statistical significance was only achieved for the objective efficacy endpoint (the change from baseline to Day 84 in inferior corneal staining score).

c) The OPUS-2 study, which was designed based on the results of the OPUS-1 study, did not meet its co-primary efficacy endpoints: change from baseline to Day 84 in inferior corneal staining score and eye dryness score measured on the visual analogue scale. Statistical significance was only achieved for the subjective efficacy end point (the change from baseline to Day 84 in eye dryness score).

7. Safety

The applicant assessed the safety of lifitegrast by pooling data into the following manner:

- All Dry Eye Studies Pool (Phase 2 Dry Eye, OPUS-1, OPUS-2 and SONATA Studies)
- 12-Week Dry Eye Studies Pool (Phase 2 Dry Eye, OPUS-1, and OPUS-2 Studies).
- The Controlled Adverse Environment (CAE) Studies Pool (Phase 2 and OPUS-1 Studies).

The safety of lifitegrast 5% after 12 weeks of dosing is presented based on the 12-Week Dry Eye Studies Pool. The safety of lifitegrast after 1 year of dosing is presented based on the SONATA Study (1118-DRY-400) safety data.

The Safety Population which included all subjects with dry eye disease who took at least 1 dose of investigational product was used for all safety analyses.

Exposure

12-Week Dry Eye Studies Pool- Safety Population

	Vehicle N=712	All LIF N=710
Total duration of treatment exposure (days)		
Mean (SD)	81.8 (12.46)	79.0 (18.04)
Standard error	0.47	0.68
Median	85.0	85.0
Min, max	1, 132	1,95
Subjects with duration of treatment exposure, n (%) [b]		
0-3 months	692 (97.2)	696 (98.0)
> 3 months	20 (2.8)	14 (2.0)

Source: CSR, Module 2.7.4 Table 6: 12 Week Dry Eye Studies Pool (Phase 2, OPUS-1, and OPUS-2 Studies)

1 Year Study – Safety Population

	Vehicle N=111	5% LIF N=220
Duration of treatment exposure (days), mean (SD)	311.3 (114.29)	304.4 (112.50)
Duration of treatment exposure, n (%)		
> 0 months	111 (100.0)	220 (100.0)
> 3 months	96 (86.5)	194 (88.2)
> 6 months	94 (84.7)	177 (80.5)
> 9 months	93 (83.8)	173 (78.6)
≥ 12 months	89 (80.2)	170 (77.3)

Source: CSR, Module 2.7.4 Table 8

Subjects were dosed twice a day in all of the dry eye studies.

Deaths

There were two deaths reported during the clinical studies with lifitegrast.

Study	Cause of Death	Patient ID	Treatment group	Duration of Exposure	Other Medical Conditions
Phase 2 dry eye	Cardiac arrest	001-125 72/M	LIF 1%	53 days	Hypercholesterolemia, hypertension
SONATA	Arrhythmia	38-004 68/F	Vehicle	54 days	Hypertension, COPD, sleep apnea

Nonfatal Serious Adverse Events

Study	Subject Number	Treatment Group	Preferred Term
Phase 2 dry eye	002-1199	Lifitegrast 0.1%	Hip fracture
Phase 2 dry eye	002-1195	Lifitegrast 0.1%	Oxygen saturation decreased
Phase 2 dry eye	001-1125	Lifitegrast 1%	Cardiac arrest
OPUS-1	12-12044	Lifitegrast 5%	Abdominal pain, upper
OPUS-1	15-15051	Lifitegrast 5%	Humerus fracture
OPUS-1	13-13017	Lifitegrast 5%	Infectious peritonitis
OPUS-1	13-13074	Lifitegrast 5%	Non-cardiac chest pain
OPUS-1	14-14011	Lifitegrast 5%	Pre-syncope
OPUS-2	65-145	Lifitegrast 5%	Renal cancer
OPUS-2	73-034	Lifitegrast 5%	Thyrotoxic crisis
OPUS-2	63-071	Lifitegrast 5%	Vertigo
SONATA	48-004	Lifitegrast 5%	Back pain, transient ischemic attack
SONATA	45-026	Lifitegrast 5%	Colonic polyp
SONATA	45-019	Lifitegrast 5%	Dysmenorrhea
SONATA	32-008	Lifitegrast 5%	Hip fracture
SONATA	38-014	Lifitegrast 5%	Myocardial infarction
SONATA	41-051	Lifitegrast 5%	Osteoarthritis
SONATA	41-020	Lifitegrast 5%	Rheumatoid arthritis
SONATA	39-002	Lifitegrast 5%	Syncope, atrioventricular block
SONATA	46-003	Lifitegrast 5%	Urinary tract infection, pneumonia
OPUS-1	15-15002	Vehicle	Intervertebral disc protrusion
OPUS-1	20-20057	Vehicle	Prostate cancer
OPUS-2	58-001	Vehicle	Bladder cancer
OPUS-2	50-052	Vehicle	Cerebrovascular accident
OPUS-2	66-031	Vehicle	Colitis ischemic
OPUS-2	65-183	Vehicle	Osteoarthritis
Phase 2 dry eye	002-1174	Vehicle	Asthma
SONATA	38-004	Vehicle	Arrhythmia
SONATA	45-004	Vehicle	Chest pain
SONATA	45-002	Vehicle	Chronic obstructive pulmonary disease
SONATA	45-014	Vehicle	Chronic obstructive pulmonary disease
SONATA	44-002	Vehicle	Intervertebral disc protrusion
SONATA	38-008	Vehicle	Spinal fracture

Source: CSR, Module 2.7.4 Table 39

The serious adverse events reported were considered not related to the investigational product. All serious adverse events resolved except for the arrhythmia which had a fatal outcome; the spinal fracture whose outcome is unknown; and COPD which resolved with sequelae. No patterns or safety concerns were raised by the reported adverse events.

Common Adverse Events

Treatment Emergent Adverse Events Occurred in >1% in Either Treatment Group All Dry Eye Studies Pool – Safety Population

System Organ Class Preferred Term	Lifitegrast N=1044 n (%)	Vehicle N=823 n (%)
Ocular TEAEs		
Subjects with ≥ 1 ocular TEAE	493 (47.2)	187 (22.7)
Eye disorders	262 (25.1)	135 (16.4)
Visual acuity reduced	66 (6.3)	48 (5.8)
Vision blurred	33 (3.2)	10 (1.2)
Lacrimation increased	29 (2.8)	4 (0.5)
Eye irritation	25 (2.4)	5 (0.6)
Eye pain	23 (2.2)	6 (0.7)
Eye pruritus	19 (1.8)	8 (1.0)
Ocular hyperemia	17 (1.6)	6 (0.7)
Conjunctival hemorrhage	12 (1.1)	4 (0.5)
Conjunctival hyperemia	12 (1.1)	10 (1.2)
Dry eye	9 (0.9)	11 (1.3)
General disorders and administration site conditions	308 (29.5)	55 (6.7)
Instillation site pain	139 (13.3)	25 (3.0)
Instillation site irritation	130 (12.5)	22 (2.7)
Instillation site reaction	113 (10.8)	8 (1.0)
Instillation site pruritus	34 (3.3)	7 (0.9)
Instillation site foreign body sensation	11 (1.1)	2 (0.2)
Instillation site lacrimation	11 (1.1)	2 (0.2)
Non-ocular TEAEs		
Subjects with ≥ 1non-ocular TEAE	355 (34.0)	184 (22.4)
Infections and Infestations	87 (8.3)	80 (9.7)
Nasopharyngitis	32 (3.1)	32 (3.9)
Sinusitis	12 (1.1)	9 (1.1)
Urinary tract infection	8 (0.8)	8 (1.0)
Nervous system disorders	175 (16.8)	23 (2.8)
Dysgeusia	143 (13.7)	3 (0.4)
Headache	25 (2.4)	6 (0.7)

Source: CSR, Module 2.7.4 Table 28
All Dry Eye Studies Pool includes the Phase 2 Dry Eye Study, OPUS-1, OPUS-2 and SONATA studies.

Safety Summary Statement

Adequate and well controlled studies support the safety of Xiidra (lifitegrast ophthalmic solution) 5% for the treatment of the signs and symptoms of dry eye disease. The most frequent treatment emergent adverse reactions which occurred in ≥ 5% of subjects and more frequently in the lifitegrast group compared to the vehicle group were: dysgeusia (14%), instillation site pain (13%), instillation site irritation (13%), instillation site reaction (11%), and visual acuity reduced (6%).

8. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9. Pediatrics

Because dry eye disease does not occur in sufficient numbers in the pediatric population, lifitegrast has not been studied in clinical studies with pediatric patients. This application was presented at the Pediatric Review Committee (PeRC) on May 14, 2015. PeRC concurred clinical studies in this population are impractical.

10. Other Relevant Regulatory Issues

REMS
The Division of Risk Management (DRISK) completed a Risk Evaluation and Mitigation Strategy (REMS) review on June 20, 2015. 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.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Xiidra, and granted conditional acceptance on April 29, 2015. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

OPDP
The Office of Prescription Drug Promotion (OPDP) did not complete a formal review of the package insert or labeling tin this review cycle. Deficiencies were identified within the application that precludes discussion of labeling at this time.

FINANCIAL DISCLOSURE
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

OSI
A routine Office of Scientific Investigations (OSI) audit was requested. The studies appear to have been conducted adequately, and the data generated by each of each of these sites appear acceptable in support of the respective indication.

11. Labeling

The application does not provide substantial evidence of efficacy. A formal labeling review is deferred until additional data is submitted to support the proposed indication.

12. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 208073, Xiidra (lifitegrast ophthalmic solution) 5%, is not recommended for approval for the treatment of the signs and symptoms of dry eye disease.

RISK BENEFIT ASSESSMENT:
Adequate and well controlled studies support the safety of Xiidra (lifitegrast ophthalmic solution) 5% for the treatment of the signs and symptoms of dry eye disease. The most frequent treatment emergent adverse reactions which occurred in ≥ 5% of subjects and more frequently in the lifitegrast group compared to the vehicle group were: dysgeusia (14%), instillation site pain (13%), instillation site irritation (13%), instillation site reaction (11%), and visual acuity reduced (6%).

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

COMPLETE RESPONSE ISSUES:
1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically:

    a) The Phase 2 Dry Eye study did not meet its primary efficacy endpoint, inferior corneal staining score at Day 84. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 84 compared to vehicle although there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.

    b) The OPUS-1 study, did not meet its co-primary efficacy endpoints; change from baseline to Day 84 in inferior corneal staining score and visual related function Ocular Surface Disease Index subscale score. Statistical significance was only achieved for the objective efficacy endpoint (the change from baseline to Day 84 in inferior corneal staining score).

    c) The OPUS-2 study, did not meet its co-primary efficacy endpoints: change from baseline to Day 84 in inferior corneal staining score and eye dryness score measured on the visual analogue scale. Statistical significance was only achieved for the subjective efficacy end point (the change from baseline to Day 84 in eye dryness score).

It is recommended that an additional clinical trial be conducted to support a demonstration of efficacy of the drug product in the intended patient population.

2. There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended or suggested in its proposed labeling. Specifically, information to support the safety of potentially having (b) (4) in the drug substance has not been submitted. Since no detectable levels (b) (4) were present in the late-stage process batches tested to date (detection limit of (b) (4) ppm), the acceptance limit should be revised to "less than (b) (4) ppm."

3. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing or holding of the drug substance are inadequate to preserve its identity, strength, quality, purity, stability and bioavailability. Specifically,

   a) The (b) (4) are not acceptable. Removal of the test (b) (4) may be requested once adequate data is available.

   b) The USP specification for particulate matter in ophthalmic solutions has been revised. The proposed acceptance criterion for particulate matter is not consistent with the current USP specification. The acceptance criteria should be revised to be consistent with the USP monograph, USP<789>.

   c) Impurities have been identified which are not being tracked. While it is claimed that most of the impurities are degradents from the drug product evidence has not been provided that these impurities originate from the drug product. The remaining unknown impurities currently claimed as leachables should be identified and qualified (i.e. provide safety data).

   d) The current specification do not account for (b) (4) unexpected issues in manufacturing. Changing the specification to all unidentified impurities and lowering the limit to the standard used for ophthalmic drug products (<0.1%) should minimize the chances that no harmful impurities (degradants, leachables or other) are included in the drug product.

   e) The Comparability Protocol (b) (4) both manufacturer and manufacturing process changes for both the drug substance and the drug product is not acceptable. The comparability protocol is not acceptable for either the proposed post-approval changes to the drug substance or the drug product. Additional data will need to be provided for a number of the proposed changes and changes to the reporting categories will need to be made. It is recommended that the Comparability Protocol be revised or deleted from the new drug application.

The following are comments/recommendations that are not approvability issues:

1. In the Amendment dated 16-Jun-2015, you provided the method validation report for *Assay, Purity, Impurities, and Identification Test by HPLC (Test Method TM.2975)*. The (b) (4) (b) (4) does not appear to give (b) (4) (b) (4) (b) (4). Thus, the HPLC method is not stability-indicating for all potential drug substance degradation pathways. Optimize the method (b) (4) for all potential degradation pathways or develop a new method that is stability-indicating.

2. The reconciliation table submitted in the amendment dated 10-Jun-2015 (table 1 of question 10) is unclear and appears to be incomplete and inaccurate. Please revise or submit new reconciliation tables taking into account the following recommendations:
   - The table should contain acceptance criteria for actual yield (minimum and maximum of the corresponding theoretical yield) for each phase of production as per CFR211.186(b)(7).
   - Provide definitions of the items listed in the first left column of the table, and indicate how they are calculated.
   - Waste/loss/rejects during manufacturing should be indicated for each step with proper explanation.
   - The actual yield for formulation (b) (4) should be the amount of solution available for filling plus that used for sampling, excluding any (b) (4)
   - Provide the actual and theoretical yield for packaging. The actual yield for this step should be (b) (4) (b) (4)
   - The reported (b) (4) is incorrect. It should be (b) (4) (b) (4) (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
10/05/2015