

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208073Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review NDA 208073

Date	June 10, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	208073
Applicant	Shire Development, LLC.
Date of Submission	January 22, 2016
PDUFA Goal Date	July 22, 2016
Proprietary Name / Established (USAN) names	Xiidra (lifitegrast ophthalmic solution) 5%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of the signs and symptoms of dry eye disease
Recommended:	Recommended for Approval

1. Introduction

Shire Development, LLC. has submitted a 505(b)(1) application for 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 (also known as CD11a/CD18 or $\alpha\text{L}\beta\text{2}$) formulated as a (b) (4) sterile eye drop without an antimicrobial preservative. Lifitegrast is thought to act by binding to LFA-1 T-cell surface antigen and minimizing interaction with its cognate ligand, ICAM-1 (also known as CD54). Lifitegrast (formerly SAR1118, SSP-005493, and SPD606) is a clear colorless to pale yellow solution for ophthalmic use. There are no ophthalmic drug products approved for the treatment of signs and symptoms of dry eye disease.

2. Background

Lifitegrast ophthalmic solution has been studied under IND 77,885 which was opened in July 2008, with the submission of a protocol for a Phase 1 study in healthy subjects. A Type B Pre-IND meeting was scheduled for October 1, 2007, to discuss the planned Phase 1 study in healthy subjects. On September 25, 2007, the Agency conveyed responses to the submitted CMC, non-clinical and clinical questions to the sponsor. On September 28, 2007, the Agency responded to additional non-clinical questions in a teleconference.

On December 15, 2010, an End-of-Phase 2 meeting was held with, SARCode Corporation, the sponsor of the IND at that time. The adequacy of the nonclinical program was discussed. Additionally, the Phase 3 clinical development plan was discussed including study design, the proposed safety study and the proposed statistical analysis. On July 6, 2011, an End-of-Phase 2

meeting was held with the Agency to discuss the drug substance and drug product synthesis, characterization and controls.

On October 1, 2012, a Type B meeting was conducted regarding the adequacy of the completed lifitegrast clinical efficacy studies to support a planned New Drug Application. The Agency recommended that at least one additional trial utilizing the final formulation and demonstrating efficacy for the objective endpoint of inferior corneal staining and a pre-specified subjective symptom be conducted and submitted in support of an NDA. On April 17, 2013, the IND sponsor, SARCode Corporation, was acquired by Shire Development, LLC.

On May 5, 2014, a Type B meeting was scheduled with CMC reviewers to discuss the content and format of the CMC and general sections of the NDA. Responses to the sponsor's questions regarding the freeze-thaw cycle studies and the droplet volume evaluation studies were conveyed. The Agency also conveyed details regarding other information expected to be included in the NDA. The meeting was cancelled by the sponsor after receiving the Agency's comments.

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. The Division communicated the expectation that studies to support an NDA should include prospectively planned endpoints which demonstrated efficacy. The Division recommended that Shire consider conducting another trial based on the information learned to date. On December 12, 2014, written responses to sponsor Pre-NDA CMC questions were conveyed.

The original NDA was submitted on February 25, 2015.

On October 16, 2015, a Complete Response letter for the original application was issued. In the Complete Response letter, the Agency conveyed issues discussed at the Late Cycle meeting including the lack of substantial evidence to support efficacy in the NDA. Additionally, there were several product quality concerns.

On December 8, 2015, an End-of-Review meeting was held. Shire provided the Agency with a summary of the OPUS-3 topline results. Shire confirmed that their resubmission application was intended to address the deficiencies listed in the Complete Response letter.

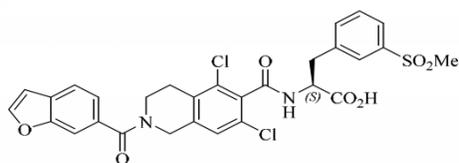
3. Product Quality

This is a new molecular entity (NME).

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))	95-105% (w/w)	HPLC
Purity by HPLC (area %)	≥96.0%	HPLC
Impurities by HPLC (b) (4) (weight %)	≤ (b) (4) %	HPLC
(b) (4) (weight %)	%	
(b) (4) (weight %)	%	
(b) (4) (weight %)	%	
(b) (4) (weight %)	%	
(b) (4) (weight %)	%	
(b) (4) (weight %)	%	UPLC
(b) (4) (weight %)		HPLC
Individual Unspecified Impurity (area%)	%	HPLC
Total impurities*		HPLC
Chiral Purity by HPLC (area %)	≥ %	HPLC
(b) (4)	≤ (b) (4) %	(b) (4)
Residual Solvents by GC (b) (4)	NMT (b) (4)	GC-FID
	NMT	
	NMT	
	NMT	
	NMT	GC-FID
	NMT	GC-FID
Residue on Ignition	NMT	USP <281>
Microbial Limit Tests		USP<61>
Total Aerobic Plate Count	≤ (b) (4) CFU/g	
Total Yeast and Mold	≤ (b) (4) CFU/g	
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 %)

Source: Module 3.2.S.4.1

Description and Composition of the Drug Product:

Table 1: Description of the Drug Product Dosage Form	
Feature	Description
Physical Description	Clear, colorless to slightly colored ophthalmic solution
Available Strength	5.0%

Source: Module 3.2.P.1

Table 2: Composition of the Drug Product Dosage Form				
Ingredient	Amount	Unit	Function	Reference to Standards
Drug substance(s)				
Lifitegrast (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid	5.0	%w/v	Active Ingredient	Module 3.2.S for NDA 208073.
Excipient(s)				
Sodium Chloride	(b) (4)	%w/v	(b) (4)	USP/NF
Sodium Phosphate Dibasic, anhydrous	(b) (4)	%w/v	(b) (4)	USP/NF
Sodium Thiosulfate, pentahydrate	(b) (4)	%w/v	(b) (4)	USP/NF
Sodium Hydroxide, (b) (4)	(b) (4)		pH adjuster	USP/NF
(b) (4)				

Table 2: Composition of the Drug Product Dosage Form				
Ingredient	Amount	Unit	Function	Reference to Standards
Hydrochloric Acid solution, (b) (4)	(b) (4)		(b) (4)	USP/NF
Water for Injection	(b) (4)		(b) (4)	USP/NF
(b) (4)	(b) (4)		(b) (4)	USP/NF
Minimum fill weight per ampule	0.20	g	Not applicable	

a Alternate concentrations may be used with appropriate adjustments to quantities.

Source: Module 3.2.P.1

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 (b) (4)	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)	(b) (4) of Label Claim	HPLC-UV Detector
Particulate Matter (b) (4)	Not More Than (b) (4) Not More Than (b) (4) Not More Than (b) (4)	USP <789>
Sterility	No growth after (b) (4) days	USP <71>
Endotoxin	Not more than (b) (4) EU/mL	USP <85>

Source: Module 3.2.P.5.1

Note: The USP acceptance criterion for the Particulate Matter specification changed to require a third criterion: Not More Than (b) (4). The proposed acceptance criterion for Particulate Matter has been revised (b) (4) with the USP monograph.

Drug Product Container Closure:

Lifitegrast ophthalmic solution, 5% utilizes a (b) (4) and an aluminum foil laminate pouch as the primary packaging system. (b) (4) and sealed (b) (4). (b) (4) are coded with the batch number and product expiry. Once formed, the (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 (b) (4) aluminum foil laminate pouch.

The (b) (4) is comprised entirely of low-density polyethylene (LDPE) and the overflow volume of each (b) (4). Each (b) (4) is filled to a target fill (b) (4) of solution, in order to ensure a nominal fill (b) (4) and that no individual (b) (4) contains less than (b) (4) of solution.

Inspections:

From the Quality Assessment addendum Review in Panorama:

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4) – API DS Mfg. and Release Testing		(b) (4)	<ul style="list-style-type: none"> NME (b) (4) sole sourced from vendor currently in import alert. 	Acceptable based upon PAI coverage
CTL - DS Microbial and Endotoxin Release and Stability			None	Acceptable based on manufacturing history
CTL - DS (b) (4) Test Release and Stability			None	Acceptable based on manufacturing history
DRUG PRODUCT				
FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
(b) (4)		(b) (4)	<ul style="list-style-type: none"> NME (b) (4), Contract manufacturer where the stability sample storage, drug product storage, and incoming packaging material storage has not been previously inspected. 	Acceptable based upon PAI coverage
Mfg. and Release Testing			None	Acceptable based on manufacturing history
CTL – DP Release and Stability Testing			None	Acceptable based on manufacturing history
(b) (4)			None	Acceptable based on manufacturing history
Secondary Packaging and Labeling			None	Acceptable based on manufacturing history

The Office of Process and Facilities (OPF) provided an overall recommendation of “acceptable” for the facilities in the Panorama on Feb 26, 2016.

See the Quality Assessment Review # 2 for NDA 208073 dated 5/2/2016 in Panorama.

Recommendation and Conclusion on Approvability

From the Quality Assessment Review # 2 for NDA 208073 dated 5/2/2016 in Panorama:

Quality micro and biopharmaceutics reviewers have recommended approval of the NDA as documented in Review #1 dated on Jul 28, 2015. As documented in this resubmission Review #2, all Complete Response issues including drug substance, drug product and process have been satisfactorily resolved. The Office of Process and Facilities (OPF) has provided an overall recommendation of “acceptable” for the facilities on Feb 26, 2016. Therefore, NDA 208073 is recommended for approval from Product Quality perspective.

An expiration dating period of 18-months is granted for Lifitegrast ophthalmic solution, 5% when packaged and stored as described in the attached labeling.

4. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 7/31/15:

Lifitegrast is a novel small-molecule antagonist of lymphocyte function-associated antigen 1 (LFA-1; also known as CD11a/CD18 or α L β 2) that is being developed by Shire as a sterile eye drop for the treatment of signs and symptoms of dry eye disease. Lifitegrast acts by inhibiting LFA-1 interaction with the cell surface glycoprotein intercellular adhesion molecule (ICAM)-1, and thereby prevents the formation of immunological synapses that are key to inflammatory cell activation and migration. The inhibition of the LFA-1/ICAM-1 interaction therefore forms the basis of the therapeutic rationale for lifitegrast as a treatment for the signs and symptoms of dry eye disease. The proposed clinical dose is 5% lifitegrast ophthalmic solution applied to each eye twice daily for a total dose of 5 mg/eye/day (50 μ L drop volume).

From the resubmission Nonclinical Pharmacology/Toxicology Review dated 4/26/16:

No new nonclinical studies were submitted in the NDA resubmission. During the first cycle review, approval was recommended pending resolution of the following issue:

“The applicant should address the request to reduce the specifications for (b) (4) to as low as reasonably possible, and to submit adequate safety data to support the levels of 3 leachables.”

These were unknown leachables with levels of (b) (4) μ g/mL found in (b) (4) stability batch 3P80 and primary stability batches 4F14-2 and 4F90-2, with relative retention times of 0.443, 0.451, and 0.451, respectively. In addition, to these 3 leachables, the Product Quality team

identified other impurities with levels above (b) (4) ppm. The nonclinical comments were conveyed to the applicant under the Product Quality complete response letter dated Oct 16, 2015.

PRODUCT QUALITY COMMENT 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) ppm of (b) (4) (b) (4) in the drug substance has not been submitted. Since no detectable levels of (b) (4) (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 5 ppm.

The applicant accepted the Agency’s comment regarding the acceptance limit for (b) (4). The drug substance specification was updated to include an acceptance criterion of not more than (b) (4) ppm (NMT (b) (4) ppm) for (b) (4).

PRODUCT QUALITY COMMENT 3

c. Impurities have been identified which are not being tracked. While it is claimed that most of the impurities are degradants 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).

Regarding the 3 leachables cited above, these were identified as (b) (4). The levels of (b) (4) are lower than the specification limit of NMT than (b) (4)% in the drug product (refer to Product Quality review). In addition, in the initial NDA, the applicant provided a rationale to justify levels (b) (4) up to (b) (4)%. Therefore, the issue is considered resolved from the nonclinical perspective.

PRODUCT QUALITY COMMENT 3

d. The current specification do not account for potential chemicals which may leach into the drug product from the packaging or may arise from 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.

The applicant used the following information (Table 1) to calculate the maximum daily dose of drug substance per day (note, slightly lower than the 5 mg/eye/day [10 mg/day] calculated by this reviewer in the 1st cycle NDA review based on a 50 µL drop volume).

Table 1: Calculation of Daily Administration of Lifitegrast Drug Substance for a Patient Treated with Lifitegrast Drug Product

(b) (4)



Per the applicant: “Based upon a daily dose of (b) (4) mg of Lifitegrast drug substance, Attachment 1 of Q3B(R2) designates an identification threshold of (b) (4) whichever is lower”. Table 2 provides information regarding the determination of which is the lower criterion (b) (4). When the criterion of (b) (4) % is applied to a daily dose of (b) (4) mg, the calculated exposure of an unidentified degradation product is (b) (4) µg/day which exceeds the (b) (4) designated in Attachment 1 of Q3B(R2). Therefore, to conform with Attachment 1 of Q3B(R2), the (b) (4) criterion should be applied for an unidentified impurity in Lifitegrast drug product. When the (b) (4) criterion is converted to percentage (Table 2), this calculation results in an acceptance criterion of (b) (4) % for an unidentified degradation product in Lifitegrast drug product. To provide a more conservative approach, an acceptance criterion of (b) (4) % for an unidentified degradation product in Lifitegrast drug product is proposed.”

Table 2: Determination of the Unidentified Impurities Identification Threshold Limit for Lifitegrast Drug Product

Parameter	Description
(b) (4)	

Pharmacology/Toxicology believes that the applicant justification is acceptable. Even if a total daily dose of 10 mg (5 mg/eye/day) is used, a specification of (b) (4) % proposed by the applicant will result in an exposure of (b) (4) µg, i.e., still at the identification threshold level. Approval is recommended.

5. Clinical Pharmacology/Biopharmaceutics

There is no new Clinical Pharmacology information provided in the resubmission. See the original Clinical Pharmacology Review dated 4/20/15

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.

The Clinical Pharmacology recommends approval.

6. Sterility Assurance

From the original Product Quality Microbiology Review (component of Quality Assessment review) dated 7/28/15.

The drug substance is not sterile; however the drug substance is controlled for microbial limits test per USP<61> and bacterial endotoxins per USP<85>. As this drug product is sterile, from review perspective, the sterility and endotoxin limits are evaluated for the drug product. The manufacturing process was validated at (b) (4) for four consecutive validation batches. The applicant concluded that the Lifitegrast manufacturing process is robust and consistently produces high purity drug substance that meets all the CQA requirements.

Lifitegrast drug substance is packaged in one low density polyethylene (LDPE) (b) (4)

Desiccant is not used.

The product release specification includes the following microbiological tests:

Test	Test Method	Acceptance	Exhibit Batch
		Criteria	Results
Bacterial Endotoxins	USP <85>	NMT (b) (4) EU/mL	NMT (b) (4) EU/mL
Sterility*	USP <71>	No growth after 14 days	Pass
Container/Closure Integrity	Pressure Decay	No leak	0 leak

*Tested on stability

No remaining product quality microbiology deficiencies were identified. Approval is recommended.

7. Clinical/Statistical - Efficacy

From the resubmission Medical Officer Review dated 4/27/16:

The original NDA submission submitted February 25, 2015, supported the safety of Xiidra (lifitegrast ophthalmic solution) 5% for the treatment of dry eye disease. Overall, Xiidra (lifitegrast ophthalmic solution) 5% was safe and well tolerated in the Phase 2 dry eye study, Studies OPUS-1, OPUS-2 and SONATA. No new safety signals were seen in the OPUS-3 study. Adverse reactions most frequently associated with lifitegrast ophthalmic solution in this application were dysgeusia, instillation site irritation, instillation site reaction, instillation site pain, visual acuity reduced, eye irritation, instillation site pruritus, lacrimation increased, vision blurred, eye pain, eye pruritus, headache, ocular hyperemia, conjunctival hyperemia, eye discharge, instillation site foreign body sensation and sinusitis.

Because the submitted studies did not fully support its efficacy, the original NDA submission received a Complete Response dated October 16, 2015. Findings from the Phase 2 Dry Eye, OPUS-1, OPUS-2 and SONATA studies were not sufficient to provide adequate evidence of efficacy for lifitegrast ophthalmic solution 5% in the twice daily dosing regimen for the treatment of dry eye disease.

In this submission which includes the OPUS-3 study, a study similar in design to the OPUS-2 study, the treatment group difference in the primary endpoint, the change from baseline to Day 84 in the eye dryness score, was statistically significant in favor of the lifitegrast group. Additionally, though the inferior corneal staining score was not a prespecified endpoint, an ad hoc analysis of the treatment group difference was performed (per the Division's request).

Analysis of Primary Endpoint(s)

OPUS-3 (Study SHP606-304)

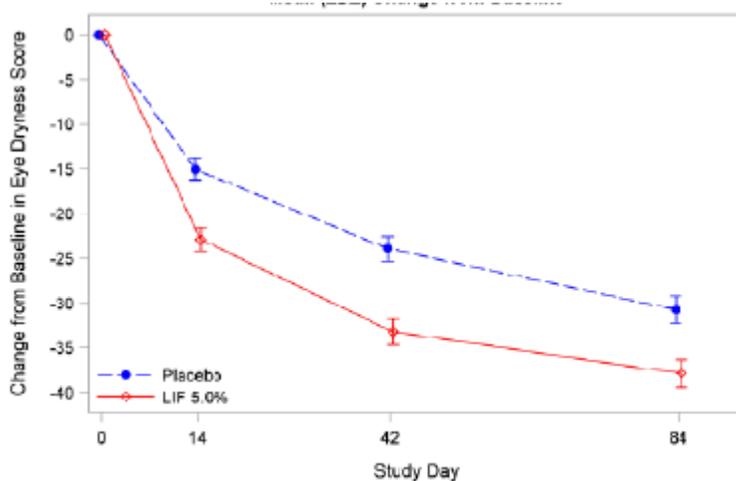
The primary endpoint was mean change from baseline to Day 84 in eye dryness score (VAS).

Table 6.1.4-1
Eye Dryness Score at Day 84 (Visual Analogue Scale)
ITT Population with LOCF

	Vehicle N=356	5% LIF N=355
Baseline (Day 0)/ Visit 2		
N	356	355
mean (SD)	69.0 (17.08)	68.3 (16.88)
Day 84 (Week 12, Visit 5)		
N	353	353
mean (SD)	38.35 (29.962)	30.43 (27.556)
Change from Baseline to Day 84		
N	353	353
Mean (SD)	-30.7 (28.01)	-37.9 (28.85)
Treatment effect (SE)		7.16 (2.096)
95% confidence interval		(3.04, 11.28)
p-value (t-test)		0.0007

Note: Eye dryness was scored on a VAS from 0-100 (0=no discomfort; 100=maximal discomfort).
 Source: OPUS-3 CSR, Table 9, Section 14, Table 3.1.1.1; Module 5.3.5.3 Table 4.1.1.

Figure 6.1.4-1
Mean Eye Dryness Score (VAS) by Treatment Group – OPUS-3
ITT Population with LOCF
Mean (± SE) Change from Baseline



ITT=intent-to-treat; LIF=lifitegrast; LOCF=last observation carried forward; SE=standard error; VAS=visual analogue scale
 Source: Section 14, Figure 1.1.1.3

In the OPUS-3 study, the lifitegrast treatment group achieved a statistically significant mean decrease from baseline to Day 84 in the eye dryness score (VAS) compared to the vehicle treatment group. The results of sensitivity analyses were consistent with the above results.

Ad Hoc Analyses on Sign Data

Because OPUS-3 was designed to replicate the symptom effect observed in OPUS-2, the applicant chose to analyze the sign assessments as safety endpoints. In response to FDA comments received on December 8, 2015, regarding the End of Review meeting, ad hoc analyses were conducted for ICSS, total corneal staining score, and nasal lissamine green staining score on the ITT population using LOCF. Results from these analyses are presented as follows:

ICSS in the Study Eye: Ad hoc analysis showed a nominally statistically significant mean improvement from baseline to Day 84 (Week 12) in ICSS for lifitegrast (-0.81) compared to vehicle (-0.64; nominal p=0.0144).

Table 6.1.6-1
Inferior Corneal Staining Score in the Study Eye
ITT Population with LOCF

	Vehicle N=356	5% LIF N=355
Baseline (Day 0)/ Visit 2		
N	356	355
mean (SD)	2.46 (0.744)	2.46 (0.681)
Day 84 (Week 12, Visit 5)		
N	351	351
mean (SD)	1.81 (1.009)	1.66 (1.044)
Change from Baseline to Day 84		
N	351	351
Mean (SD)	-0.64 (0.915)	-0.81 (0.941)
Treatment effect (SE)		0.17 (0.069)
95% confidence interval		(0.03, 0.30)
p-value ^a		0.0144

^a p-value from the ANOVA model of change with treatment, stratum and treatments by stratum interaction; weights were set to stratum size.

Note: Corneal staining was scored as follows: 0=no staining/none; 1=occasional/trace; 2=countable/mild; 3= uncountable, but not confluent/moderate; 4=confluent/severe.

Source: Module 5.3.5.3, Table 3.1.1.

Total Corneal Fluorescein Staining Score in the Study Eye:

An ad hoc analysis showed that lifitegrast and vehicle groups had similar mean improvements (-1.68 and -1.36, respectively) in total corneal fluorescein staining score from baseline to Day 84 (Week 12) (nominal $p=0.0520$).

Nasal Lissamine Staining Score in the Study Eye:

An ad hoc analysis showed that lifitegrast and vehicle groups had similar mean improvements (-0.34 and -0.24, respectively) in nasal lissamine staining score from baseline to Day 84 (Week 12) (nominal $p=0.1402$).

An ad hoc analysis of the treatment group difference was performed (per the Division's request at the End of Review meeting) for the change from baseline to Day 84 for the ICSS. This analysis demonstrated results similar in magnitude to that seen in the Phase 2 and OPUS-1 studies in favor of lifitegrast and a nominal p -value of 0.0144.

Summary Efficacy Statement

The application provides substantial evidence of efficacy for lifitegrast ophthalmic solution, 5%, in the treatment of dry eye disease.

In this submission which includes the OPUS-3 study, a study similar in design to the OPUS-2 study, the treatment group difference in the primary endpoint, the change from baseline to Day 84 in the eye dryness score, was statistically significant in favor of the lifitegrast group. Additionally, though the inferior corneal staining score was not a prespecified endpoint, an ad hoc analysis of the treatment group difference was performed (per the Division's request) and demonstrated results in favor of lifitegrast and a nominal p -value of 0.0144.

In summary, efficacy for the treatment of dry eye disease has now been demonstrated by replication of the sign and symptom endpoints achieved in the submitted studies of lifitegrast compared to vehicle. The results are as follows:

- A statistically significant treatment response in the objective sign endpoint, change from baseline to Day 84 in inferior corneal staining score, was demonstrated in the Phase 2 and OPUS-1 studies. Additional replication was seen in the ad hoc analysis in OPUS-3 which showed nominally statistically significance for the same sign endpoint.
- A statistically significant treatment response for the subjective symptom endpoint, change from baseline in eye dryness score (VAS), was demonstrated in the OPUS-2 and OPUS-3 studies. The treatment effect in this symptom favoring lifitegrast was also observed in a post hoc analysis of the OPUS-1 study in a subgroup of subjects similar to those enrolled in OPUS-2 and OPUS-3. Improvement in Eye Dryness Score (EDS) symptoms in subjects treated with lifitegrast compared to vehicle was observed as early as Day 14 in OPUS-2 and OPUS-3.

8. Safety

Reference is made to the original submission NDA 208-073 for Xiidra (lifitegrast ophthalmic solution) 5% for the signs and symptoms of dry eye disease (DED) submitted on February 25, 2015, which received a Complete Response Letter on October 16, 2015. In the original submission the safety of Xiidra (lifitegrast ophthalmic solution) 5% was demonstrated in the findings from the Phase 2 Dry Eye, OPUS-1, OPUS-2 and SONATA studies.

After receiving pre-submission feedback from the Division, the OPUS-3 study was designed by the applicant to demonstrate efficacy in resolution of an ocular symptom, eye dryness score. The safety data from OPUS-3 are consistent with that seen in the previous studies. No new safety signals were seen in this study.

**Table 7.1.1-1
 Summary of Completed Clinical Studies for Lifitegrast Ophthalmic Solution, 5%**

Study Identifier	Study Description	Treatment Group	Dosing Regimen/ Duration	Endpoints
Phase 1				
Study SAR 1118-001 PK and Safety	Randomized, double-masked, vehicle-controlled dose-escalation study	Lifitegrast 0.1, 0.3, 1, 5% or vehicle ophthalmic solution 28 healthy subjects (28 males/ 0 females) (20 subjects on lifitegrast)	21 days of treatment separated by observation days <u>Period 1:</u> single dose, 1 drop (1 day observation) <u>Period 2:</u> 1 drop BID (10 days observation) <u>Period 3:</u> 1 drop TID (10 days observation)	PK: Descriptive PK analysis of tear and blood samples Safety: Adverse events, clinical labs, vital signs, ECGs, physical exams, ophthalmic exams
Phase 2				
Study 1118-ACJ-100 Allergic conjunctivitis study	Phase 2, single center, randomized, prospective, double-masked, vehicle-controlled, modified CAC study	Lifitegrast 0.1, 1, or 5% or vehicle ophthalmic solution 60 subjects with allergic conjunctivitis (31 males/ 29 females) 45 subjects on lifitegrast	Single eye 1 drop TID for 14 days (2 weeks)	PK: Descriptive PK analysis of blood samples Safety: Adverse events, clinical labs, lymphocyte counts, drop comfort, BCVA, SLE, DFE, corneal endothelial cell counts

Study Identifier	Study Description	Treatment Group	Dosing Regimen/ Duration	Endpoints
Study 1118-KCS-100 Safety and Efficacy	Multicenter, randomized, prospective, double-masked, vehicle-controlled parallel arm study	Lifitegrast 0.1% (N=57) Lifitegrast 1% (N=57) Lifitegrast 5% (N=58) Vehicle (N=58) 230 subjects with dry eye disease (51 males/ 179 females)	1 drop BID for 84 days (12 weeks)	Single primary endpoint of ICSS (sign in the study eye) at Day 84 (Week 12)
Phase 3				
Study 1118-KCS-200 (SPD606-301; OPUS-1) Safety and Efficacy	Multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution 588 subjects (142 males/ 446 females)	Single eye 1 drop BID for 84 days (12 weeks)	Coprimary endpoints of ICSS (sign) and VR-OSDI score (symptom), each analyzed by mean change from baseline to Day 84 (Week 12)
Study 1118-DRY-300 (SPD606-302; OPUS-2) Safety and Efficacy	Multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution 718 subjects (168 males/ 550 females)	Single eye 1 drop BID for 84 days (12 weeks)	Coprimary endpoints of ICSS (sign) and EDS score (symptom), each analyzed by mean change from baseline to Day 84 (Week 12)
Study 1118-DRY-400 (SPD606-303; SONATA) Safety	Phase 3, multi-center, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution 332 subjects with dry eye disease (82 males/ 250 females)	Single eye 1 drop BID for 360 days	PK: Descriptive PK analysis of blood samples Safety: Adverse events, clinical labs, lymphocyte counts, drop comfort, BCVA, SLE, DFE, corneal endothelial cell counts
Study SHP606-304 (OPUS-3) Efficacy	Phase 3, multi-center, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution 711 subjects with dry eye disease (174 males/ 537 females)	Single eye 1 drop BID for 84 days	Efficacy: Primary symptom endpoint: eye dryness score (EDS) analyzed by mean change from baseline to Day 84 (Week 12). No primary sign endpoint.

The applicant assessed the safety of lifitegrast by pooling data from the following studies:

- One Phase 2, double-masked, vehicle-controlled, 12-week, efficacy and safety study (Phase 2 Dry Eye)
- Three Phase 3, double-masked, vehicle-controlled, 12-week, efficacy and safety studies (OPUS-1, OPUS-2 and OPUS-3)
- One Phase 3, double-masked, vehicle-controlled, 1 year, safety study (SONATA).

Deaths

In the original submission, there were two deaths reported during the clinical studies with lifitegrast. One death occurred during the Phase 2 dry eye study and the other during the SONATA safety study.

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

Common Adverse Events

Table 7.4.1-1
Treatment Emergent Adverse Events Occurred in >5% in Either Treatment Group
OPUS-3 – Safety Population

System Organ Class Preferred Term	Vehicle N=354 n (%)	5% LIF N=357 n (%)
Ocular TEAEs		
Subjects with ≥ 1 ocular TEAE	63 (17.8)	141 (39.5)
General disorders and administration site conditions		
Instillation site irritation	11 (3.3)	65 (18.2)
Instillation site reaction	19 (5.4)	45 (12.6)
Non-ocular TEAEs		
Subjects with ≥ 1 non-ocular TEAE	29 (8.2)	84 (23.5)
Nervous system disorders		
Dysgeusia	1 (0.3)	46 (12.9)

Source: CSR, Module 5.3.5.1 Tables 15 and 16

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.

In the OPUS-3 study, the treatment emergent adverse reactions which occurred in $\geq 5\%$ of subjects and more frequently in the lifitegrast group compared to the vehicle group were: dysgeusia (13%), instillation site irritation (18%), and instillation site reaction (13%).

Table 7.4.1-4: Treatment Emergent Adverse Events Occurring in $\geq 1\%$ 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.

In the All Dry Eye Studies safety population, the treatment emergent adverse reactions which more frequently in the lifitegrast 5% group compared to the vehicle group (highlighted above) and occurred in 5-25% of subjects were: instillation site irritation, dysgeusia, and visual acuity reduced.

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.

The adverse event profile seen in OPUS-3 was similar to that seen in the previous clinical studies. No new safety signals were revealed.

Nonfatal Serious Adverse Events

Reference is made to the original submission NDA 208-073 for Xiidra (lifitegrast ophthalmic solution) 5% for the signs and symptoms of dry eye disease (DED). No new safety signals were seen in this study.

Table 7.3.2-1
Serious Treatment Emergent Adverse Events
Safety Population – OPUS-3

Preferred Term	Vehicle N=354 n (%)	5% LIF N=357 n (%)
Subjects with ≥ 1 serious TEAE	4 (1.1)	4 (1.1)
Accelerated hypertension	1 (0.3)	0
Basal cell carcinoma	1 (0.3)	0
Cerebrovascular accident	0	1 (0.3)
Lower limb fracture	1 (0.3)	0
Lung neoplasm malignant	0	1 (0.3)
Periprosthetic fracture	1 (0.3)	0
Pneumonia	0	1 (0.3)
Transient ischemic attack	0	1 (0.3)

Source: CSR, Module 5.3.5.1 Table 20

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. The treatment emergent adverse reactions which more frequently in the lifitegrast 5% group compared to the vehicle group and occurred in 5-25% of subjects were: instillation site irritation, dysgeusia, and visual acuity reduced. 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.

The SONATA study was designed to assess the long term safety profile of Xiidra (lifitegrast ophthalmic solution) 5% dosed twice daily for 360 days in dry eye patients under actual use circumstances (i.e., patients could use artificial tears, topical ophthalmic or nasal steroids, antihistamines, mast cell stabilizers, and contact lenses after Day 14, as needed). The safety profile seen in SONATA was similar to that observed in the other adequate and well controlled studies.

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

BIOSTATISTICS

Per the Biostatistics review dated 5/25/16 for the resubmission:

On January 22, 2016, the applicant re-submitted NDA application for lifitegrast for the treatment of the signs and symptoms of DED in adults administered twice a day (AM and PM) into each eye. The re-submission included efficacy and safety results from a single Phase 3 OPUS-3 study.

The applicant main efficacy analyses in each study compared the mean change in EDS and the mean change in ICSS between the LIF 5% and Placebo treated groups, but the studies varied in the statistical analyses methods used to evaluate the treatment differences (See Table below).

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 ($\leq 1.0 / > 1.0$)	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

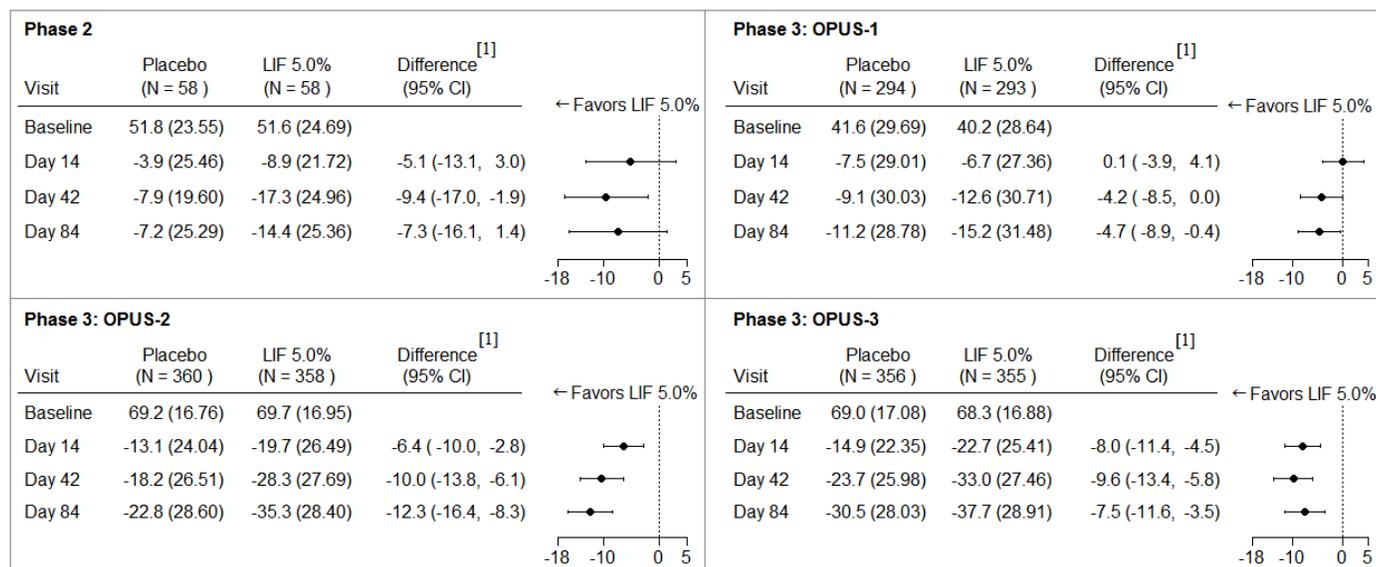
^[1]: **Seven** subjects in the Phase 2 study for both EDS and ICSS, and **five** subjects for EDS and **nine** subjects for ICSS in OPUS-3 study with only baseline values were excluded in the applicant efficacy analysis

As such, for ease of across study assessment, analysis of covariance (ANCOVA) model was used in this review 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



^[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, subjects treated with lifitegrast demonstrated statistically superior improvement in the primary clinical symptom of DED early on and continued improvement throughout the study compared to placebo treated subjects. At the end of the treatment period on Day 84, the improvement in clinical symptom seen in the LIF 5% treated group was higher than in the placebo treated group by about 12 units in the OPUS-2 study, 8 units in the OPUS-3 study, 5 units in the OPUS-1 study, and 7 units in the Phase 2 study.

Therefore, based on the primary efficacy evidences for symptom in the OPUS-2 and OPUS-3 studies and the supportive evidences in the Phase 2 and OPUS-1 studies, treatment with lifitegrast ophthalmic solution 5% demonstrated substantial efficacy evidence in improving the clinical symptoms of DED compared to placebo.

Efficacy Evidence for Clinical Sign of DED

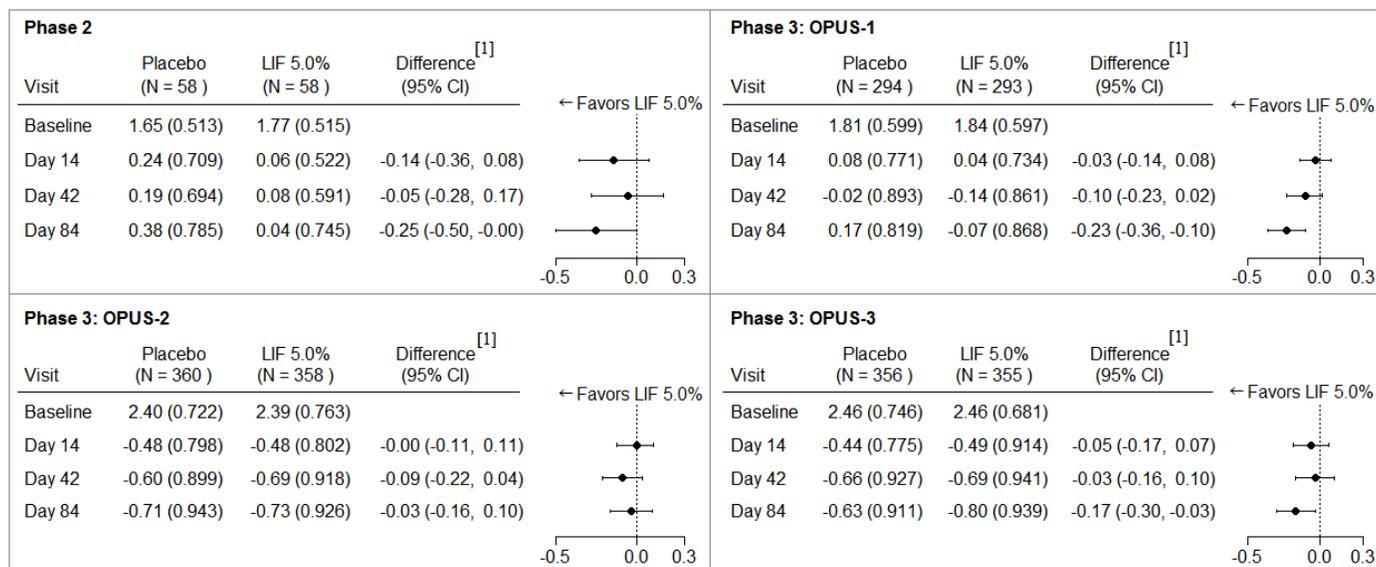
The summary of the mean change in ICSS from baseline over time and the treatment differences (95% CI) based on the ANCOVA model are shown in Figure 2 below for each study.

In the Phase 2 and OPUS-1 studies, placebo treated subjects showed worsening in clinical sign (as measured in ICSS) at Day 84 whereas LIF 5.0% treated subjects in these studies showed no change from baseline on average. In both studies, the mean reduction in ICSS at Day 84 in the treatment arm was higher than in the placebo arm by about a quarter unit, and this difference was statistically significant in the OPUS-1 study ($p < 0.001$) and was marginally significant in the Phase 2 study ($p = 0.048$).

In the OPUS-2 and OPUS-3 studies, both placebo and LIF 5% treated subjects demonstrated at least half unit improvement early on (at Day 14) and continued improving throughout the study. At the end of the treatment period on Day 84; both groups in OPUS-2 study showed equal amount of improvement (about 0.7 units) from baseline on average, and LIF 5% treated group in OPUS-3

showed about 0.8 unit improvement from baseline while placebo treated group showed about 0.6 unit improvement from baseline.

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



^[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.

Therefore, based on the primary efficacy evidences for clinical sign in the Phase 2 and OPUS-1 studies, and the supportive evidence in the OPUS-2 and OPUS-3 studies, treatment with lifitegrast ophthalmic solution 5% demonstrated better efficacy benefit in maintaining or improving the clinical sign of DED (as measured in ICSS) compared to placebo.

Safety Evaluation

In terms of safety evaluation, the test product was well-tolerated. No ocular serious adverse event was reported in each study; most common ocular adverse events, mostly reported in the treatment arm, were *instillation site complaints* such as *site irritation*, *site pain*, and *site reaction*.

Based on my review of the three studies included in the original NDA submission (Phase 2, OPUS-1, and OPUS-2) and the additional efficacy data from the OPUS-3 study, lifitegrast ophthalmic solution 5.0% demonstrated evidence of efficacy for the treatment of signs (as measured in ICSS) and symptoms (as measured in EDS) of dry eye disease in adult subjects.

REMS

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

The DRISK and DTOP concurred 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.

DMEPA

In this review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Xiidra, and granted conditional acceptance on 3/10/16. 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) completed a formal review of the package insert and labeling on 5/9/16. OPDP attended the 5/17/16 labeling meeting for this application.

DMPP

The Division of Medical Policy Programs (DMPP) completed a collaborative patient labeling review written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) on 5/9/2016. OPDP attended the 5/17/16 labeling meeting for this application.

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 in the original NDA review cycle. During this cycle, no additional inspections were conducted of the OPUS-3 study investigators.

Per the OSI review dated June 26, 2015:

These sites were selected for inspection as they were among the higher enrollers for their respective studies.

RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
John Lonsdale, M.D. Central Maine Eye Care 181 Russell St. Lewiston, ME 04240	1118-KCS- 200/ 12/ 80	20-24 Apr 2015	NAI
Robert Smyth-Medina, M.D. North Valley Eye Medical Group	1118-DRY-300/ 65/	20, 21 Apr 2015	NAI

11550 Indian Hills Rd, Suite 341 Mission Hills, CA 91345	49		
Kelly Nichols, O.D. University of Houston 505 J. Davis Armistead Building Houston, TX 77204	1118-DRY-400/ 41/ 30	11-20 May 2015	NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of

EIR is pending.

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.

DIVISION OF PEDIATRIC AND MATERNAL HEALTH

The Division of Pediatric and Maternal Health Memorandum on pregnancy and lactation labeling was completed on 9/16/15 in the original NDA review cycle. . The terms “embryotoxicity” and “teratogenicity” appear to be used as separate terms in error. Embryotoxicity should be considered to be a subset of teratogenicity in the review.

12. Labeling

NDA 208073, Xiidra (lifitegrast ophthalmic solution) 5%, is recommended for approval for the treatment of the signs and symptoms of dry eye disease with the labeling attached as an Appendix in this review. .

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:

NDA 208073, Xiidra (lifitegrast ophthalmic solution) 5%, is recommended for approval for the treatment of the signs and symptoms of dry eye disease.

RISK BENEFIT ASSESSMENT:

The application provides substantial evidence of efficacy for lifitegrast ophthalmic solution, 5%, in the treatment of dry eye disease.

In this submission which includes the OPUS-3 study, a study similar in design to the OPUS-2 study, the treatment group difference in the primary endpoint, the change from baseline to Day 84 in the eye dryness score, was statistically significant in favor of the lifitegrast group. Additionally, though the inferior corneal staining score was not a prespecified endpoint, an ad hoc analysis of the treatment group difference was performed (per the Division’s request) and demonstrated

results in favor of lifitegrast and a nominal p-value of 0.0144. In summary, efficacy for the treatment of dry eye disease has now been demonstrated by replication of the sign and symptom endpoints achieved in the submitted studies of lifitegrast compared to vehicle.

Adequate and well controlled studies (Phase 2 Dry Eye, OPUS-1, OPUS-2, OPUS-3 and SONATA Studies) support the safety of Xiidra (lifitegrast ophthalmic solution) 5% for the treatment of the signs and symptoms of dry eye disease. The treatment emergent adverse reactions which more frequently in the lifitegrast 5% group compared to the vehicle group and occurred in 5-25% of subjects were: instillation site irritation, dysgeusia, and visual acuity reduced. 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.

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.

Appendix

NDA 208073, Xiidra (lifitegrast ophthalmic solution) 5%, is recommended for approval for the treatment of the signs and symptoms of dry eye disease with the package insert and patient labeling submitted on 6/10/16 and carton and container labeling submitted on 5/16/16.

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

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

/s/

WILLIAM M BOYD
06/13/2016

WILEY A CHAMBERS
06/17/2016