

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208073Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL OUTCOME ASSESSMENTS CONSULT REVIEW

Template version: June 24, 2015

<b>COA TRACKING NUMBER</b>	2016-024
<b>IND/NDA/BLA NUMBER</b>	NDA 208073
<b>LETTER DATE/SUBMISSION NUMBER</b>	2
<b>PDUFA GOAL DATE</b>	
<b>DATE OF CONSULT REQUEST</b>	08 February 2016
<b>REVIEW DIVISION</b>	Division of Transplant and Ophthalmology (DTOP)
<b>MEDICAL REVIEWER</b>	Rhea Lloyd, M.D.
<b>REVIEW DIVISION PM</b>	Christina Marshall
<b>CLINICAL OUTCOME ASSESSMENT (COA) REVIEWER(S)</b>	Selena Daniels, Pharm.D, MS
<b>ASSOCIATE DIRECTOR, COA (ACTING)</b>	Elektra Papadopoulos, M.D., MPH
<b>REVIEW COMPLETION DATE</b>	13 June 2016
<b>ESTABLISHED NAME</b>	Lifitegrast ophthalmic solution
<b>TRADE NAME</b>	Xiidra
<b>APPLICANT</b>	Shire
<b>CLINICAL OUTCOME ASSESSMENT TYPE</b>	Patient-reported Outcome
<b>ENDPOINT(S) CONCEPT(S)</b>	Eye Dryness; Eye Discomfort
<b>MEASURE(S)</b>	Visual Analog Scale (VAS) Symptom Index: Eye Dryness score, Eye Discomfort score; Ocular Discomfort Score (ODS)
<b>INDICATION</b>	Treatment of dry eye disease (DED)
<b>INTENDED POPULATION(S)</b>	Adults with DED
<b>NOTE</b>	This NDA review examined PRO assessments in Studies 1118-DRY-300 (OPUS-2) and SHP606-304 (OPUS-3) rather than a dossier submission.

## Clinical Outcome Assessment Review

Selena R. Daniels, PharmD, MS

NDA 208073

Lifitegrast ophthalmic solution

VAS symptom index-Eye Dryness score; Eye Discomfort score; ODS

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### A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) abbreviated review is provided as a response to a request for consultation by the Division of Transplant and Ophthalmology (DTOP) regarding NDA 208073: lifitegrast ophthalmic solution for the treatment of (b) (4) dry eye disease (DED).

According to the applicant's submission, subjective symptoms of DED (e.g., patient-reported eye dryness and discomfort) are the most striking features of the disease and often times the only factor upon which the diagnosis is based on.

DTOP requested COA Staff to review patient reported outcome (PRO) assessments used as key study endpoints in Studies 1118-DRY-300 (OPUS-2) and SHP606-304 (OPUS-3) to assess symptoms of DED.

The PRO assessments include:

- Visual Analog Scale (VAS) symptom index-Eye Dryness score; Eye Discomfort score (Appendix A)
- Ocular Discomfort Score (ODS) (Appendix B)

The Division had previously agreed on the acceptability of the VAS symptom index and ODS before COA Staff consultation. Specifically, there was agreement that the Eye Dryness score was acceptable for use as a primary endpoint (co-primary endpoint in OPUS-2; primary endpoint: OPUS-3) and secondary endpoint (OPUS-3). Additionally, there was agreement that the Eye Discomfort score and ODS was acceptable for use as secondary endpoints (OPUS-2). The lifitegrast program appears to use patient-reported questionnaires that were similar to methods previously accepted by the Division for evaluation of topical ophthalmic products. Therefore, the review focused on whether the instruments were fit-for-purpose in the context of this particular drug development program to assess symptoms of DED in the clinical trial. The clinical review provides further details of the study designs.

The submission did not include an evidence dossier describing the development of the PRO instruments. This review concludes that based on face validity, these instruments measure the appropriate key symptoms of patient-reported dry eye and discomfort and appear fit-for purpose for this drug development program.

**Clinical Outcome Assessment Review**

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VAS symptom index-Eye Dryness score; Eye Discomfort score; ODS

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**APPENDIX A: Visual Analog Scale-Symptom Index**

**Visual Analogue Scale (VAS)**

Subjects will be asked the following questions regarding their current ocular discomfort (unrelated to study drug instillation) at all visits.

The subject will be asked to subjectively rate each ocular symptom (OU) by placing a vertical mark on the horizontal line to indicate the level of discomfort. 0% corresponds to “no discomfort” and 100% corresponds to “maximal discomfort.”

<b>Burning/Stinging</b>	0%	50%	100%
	-----		
<b>Itching</b>	0%	50%	100%
	-----		
<b>Foreign body sensation</b>	0%	50%	100%
	-----		
<b>Eye Discomfort</b>	0%	50%	100%
	-----		
<b>Eye Dryness</b>	0%	50%	100%
	-----		
<b>Photophobia</b>	0%	50%	100%
	-----		
<b>Pain</b>	0%	50%	100%
	-----		

**Clinical Outcome Assessment Review**

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VAS symptom index-Eye Dryness score; Eye Discomfort score; ODS

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**APPENDIX B: Ocular Discomfort Score**

**Ocular Discomfort Score (ODS) Assessment**

**Assessment of ocular discomfort scores will be conducted by site personnel and will be subjectively graded by the subjects according to the following scale (rating each eye separately):**

*At this moment in time - rate the discomfort level of each eye*

No discomfort	0
Slight discomfort or awareness	1
Mild discomfort or awareness	2
Moderate discomfort	3
Severe discomfort	4

*Reference: modified from Begley, (2003), Invest Ophthalmol Vis Sci and Caudle, (2007), Opt and Vis Sci*

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/s/  
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SELENA R DANIELS

06/13/2016

ELEKTRA J PAPADOPOULOS

06/23/2016

## CLINICAL REVIEW

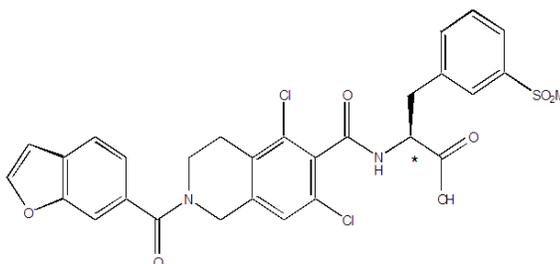
Application Type NDA  
Application Number(s) 208-073  
Priority or Standard Priority

Submit Date(s) January 22, 2016  
Received Date(s) January 22, 2016  
PDUFA Goal Date June 22, 2016  
Division / Office DTOP/OAP

Reviewer Name(s) Rhea A. Lloyd, MD  
Review Completion Date April 26, 2016

Established Name lifitegrast ophthalmic solution, 5%  
(Proposed) Trade Name Xiidra  
Therapeutic Class LFA-1 antagonist  
Applicant Shire Development, LLC.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5637  
866-744-7362

Formulation(s)



Dosing Regimen Instill 1 drop in the affected eye(s) twice a day, approximately 12 hours apart  
Indication(s) Treatment of dry eye disease.  
Intended Population(s) Adults with dry eye disease

Template Version: March 6, 2009

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Clinical Review  
Rhea A. Lloyd, MD  
NDA 208-073

Lifitegrast ophthalmic solution, 5%

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

NDA 208-073 is recommended for approval from a clinical perspective.

The studies submitted in the original NDA submission, February 25, 2015, and in response to the October 16, 2015, Complete Response Letter were successful in demonstrating safety and effectiveness in the treatment of dry eye disease.

Reviewer's Comments are in italics.

### 1.2 Risk Benefit Assessment

*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) 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 four submitted studies of lifitegrast compared to vehicle. The results are as follows:*

- A statistically significant treatment response for 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 statistical 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.*

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Lifitegrast ophthalmic solution 5% is an antagonist of LFA-1 (also known as CD11a/CD18 or  $\alpha L\beta 2$ ) formulated as an unpreserved (b) (4) sterile eye drop. Lifitegrast binds to LFA-1 targets T-cell surface antigen and prevents interaction with its cognate ligand, ICAM-1 (also known as CD54). Lifitegrast is not an immunosuppressant.

Lifitegrast (formerly SAR1118, SSP-005493, and SPD606) is a sterile, clear, colorless to pale yellow solution for ophthalmic use. The active ingredient is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl) propanoic acid.

Established Name:	lifitegrast ophthalmic solution 5%
Proposed Trade Name:	Xiidra
Chemical Class:	new molecular entity
Pharmacological Class:	LFA-1 antagonist
Indication:	treatment of the signs and symptoms of dry eye disease
Dosing Regimen:	Instill 1 drop twice a day in the affected eye(s) using a single (b) (4)
Age Groups:	Adults with dry eye disease

**Table 2.1-1 Composition of Lifitegrast Ophthalmic Solution**

<b>Component</b>	<b>Concentration % w/v</b>	<b>Function</b>	<b>Reference to Quality Standards</b>
Lifitegrast	5.0	Active ingredient	(b) (4) CoA standards
Sodium Chloride	(b) (4)	(b) (4)	USP/NF
Sodium Phosphate Dibasic, anhydrous	(b) (4)	(b) (4)	USP/NF
Sodium Thiosulfate, pentahydrate	(b) (4)	(b) (4)	USP/NF
Sodium Hydroxide	(b) (4)	pH adjuster	USP/NF
(b) (4)	(b) (4)	(b) (4)	USP/NF
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

a Alternate concentrations may be used with appropriate adjustments to quantities

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are no ophthalmic drug products approved for the treatment of dry eye disease.

## 2.3 Availability of Proposed Active Ingredient in the United States

Lifitegrast is a new molecular entity that has not been approved in the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs

None.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Lifitegrast ophthalmic solution has been studied under IND 77885 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 in order to reach agreement regarding the adequacy of the completed lifitegrast clinical efficacy studies to support a planned New Drug Application. The Agency recommended conducting at least one additional trial utilizing the final formulation, confirming efficacy for the objective endpoint of inferior corneal staining and demonstrating efficacy for a prespecified subjective symptom.

On April 17, 2013, the IND sponsor, SARCode Corporation, was acquired by Shire Development, LLC. Correspondence regarding the IND was to continue to be with SARCode Bioscience.

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 would 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 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, a Type A 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.

## 2.6 Other Relevant Background Information

None.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

*There is no evidence that the studies reviewed in this application were not conducted in accordance with acceptable clinical ethical standards. During the review of the original NDA submission, three study sites were inspected and classified NAI. During this cycle, no additional inspections were conducted of the OPUS-3 study investigators.*

### 3.2 Compliance with Good Clinical Practices

The studies performed under IND 77,885 [Phase 2 Dry Eye Study (Study 1118-KCS-100) OPUS-1 (Study 1118-KCS-200), OPUS-2 (Study 1118-DRY-300), SONATA (Study 1118-DRY-400)] and OPUS-3 (SHP606-304) were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki.

Before initiation of the studies, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The study began after receiving written approval from each EC/IRB.

### 3.3 Financial Disclosures

See Section 9.3 of this review.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Lifitegrast ophthalmic solution 5% is a sterile solution filled in unit-dose (b) (4) to be administered topically to the eye. It is contained in unit-dose (b) (4) (b) (4) low-density polyethylene. A card of 5 (b) (4) is packaged in aluminum foil laminate pouches. Multiple foil pouches are packaged in a paperboard carton.

The formulation is a non-preserved, isotonic unit-dose ophthalmic. The formulation is adjusted to a pH of 7.0 – 8.0 with sodium hydroxide and/or hydrochloric acid.

**Table 4.1-1  
Specifications for Lifitegrast Ophthalmic Solution, 5.0%**

Test	Acceptance Criteria	Analytical Procedure
Appearance <sup>a</sup>	Clear, colorless to slightly colored solution	Visual Inspection
Color <sup>a</sup>	(b) (4)	USP <631>
pH <sup>a</sup>	7.0 – 8.0	USP <791>
Osmolality <sup>a</sup>	200-330 mOsm/kg	USP <785>
Lifitegrast Assay <sup>a</sup>	(b) (4) of Label Claim	HPLC-UV Detector
Degradation Products <sup>a</sup>		
Any Unidentified Degradation Product	Not more than (b) (4) %	HPLC-UV Detector
Total Degradation Products	Not more than (b) (4) %	
Identification A: HPLC Retention Time	The retention time of the major peak of the sample corresponds to the lifitegrast peak in the reference standard solution.	HPLC-UV Detector
Identification B: UV Spectrum	The sample and reference HPLC peaks exhibit the same UV spectra from 200-400 nm.	HPLC-UV Diode Array
Minimum Fill Volume		USP <755>
Mean content	Not less than (b) (4) mL	
Content of any Single Container	Not less than (b) (4) mL	
Sodium Thiosulfate Assay	(b) (4) % of Label Claim	HPLC-UV Detector
Particulate Matter (b) (4) <sup>a</sup>	Not more than (b) (4)	USP <789>
	Not more than (b) (4)	
	Not more than (b) (4)	
Sterility <sup>a</sup>	No growth after (b) (4) days	USP <71>
Endotoxin <sup>a</sup>	Not more than (b) (4) U/mL	USP <85>

<sup>a</sup> Tested on stability; <sup>b</sup> The acceptance criterion is based upon analysis relative to (b) (4) reference solutions prepared as described in the current European Pharmacopoeia, Section 2.2.2. "Degree of Coloration of Liquids".

## 4.2 Clinical Microbiology

*There is no clinical microbiology review for this product. It is not an anti-infective.*

## 4.3 Nonclinical Pharmacology/Toxicology

This Resubmission after Complete Response does not include new Pharmacology Toxicology data.

## 4.4 Clinical Pharmacology

This Resubmission after Complete Response does not include new Clinical Pharmacology data.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

Reference is made to the original submission of NDA 208-073 for Xiidra (lifitegrast ophthalmic solution) 5.0% for the treatment of dry eye disease which contained data for the following studies: Phase 2 Dry Eye Study (1118-KCS-100), two Phase 3 Dry Eye Studies [1118-KCS-200 (OPUS-1) and 1118-DRY-300 (OPUS-2)] and a longer term safety study (1118-DRY-400; SONATA). The Medical Officer's review for this submission was finalized on August 12, 2015.

A Complete Response letter was issued on October 16, 2015. In the Complete Response letter, the Agency requested that data from an additional clinical trial be submitted to provide substantial evidence of efficacy of the drug product in the intended patient population. This Resubmission includes data from an additional clinical trial OPUS-3, as requested.

**Summary of the Clinical Study Submitted in this Resubmission**

Study Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Phase 3</b>					
<b>Study SHP606-304 (OPUS-3)</b>  Safety and Efficacy	<u>Primary:</u> To evaluate efficacy assessed by eye dryness score (EDS) (mean change from baseline to Day 84)  <u>Key Secondary Endpoints:</u> To evaluate efficacy as measured by EDS (mean change from baseline to Day 42)  To evaluate efficacy as measured by EDS (mean change from baseline to Day 14)	Phase 3, multicenter, randomized, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution  711 subjects (174 males/ 537 females)	Single eye 1 drop BID for 84 days (12 weeks)	Primary efficacy endpoint: EDS score (symptom) analyzed by mean change from baseline to Day 84 (Week 12)

**Summary of Clinical Studies for Lifitegrast Ophthalmic Solution, 5%  
Reviewed in Original NDA Submission**

<b>Study Identifier</b>	<b>Study Objective</b>	<b>Study Design</b>	<b>Treatment Group</b>	<b>Dosing Regimen/ Duration</b>	<b>Endpoints</b>
<b>Phase 1</b>					
<b>Study 1118-001</b>  PK and Safety	<u>Primary:</u> To assess safety and tolerability  <u>Secondary:</u> To determine the PK profile in plasma and tears	Randomized, double-masked, vehicle-controlled dose-escalation study	Lifitegrast 0.1, 0.3, 1.0, 5% or vehicle ophthalmic solution  28 healthy subjects (28 males/ 0 females)	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
<b>Phase 2</b>					
<b>Study 1118-KCS-100</b>  Dose-Ranging, Safety and Efficacy  (Phase 2 Dry Eye Study)	<u>Primary:</u> To evaluate the efficacy assessed by ICSS at Day 84 <u>Secondary:</u> To evaluate subjective and objective efficacy measures with and without the CAE; To evaluate safety and tolerability	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)

Study Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Phase 3</b>					
<b>Study 1118-KCS-200</b> (SPD606-301; OPUS-1)  Safety and Efficacy	<u>Primary:</u> To evaluate efficacy assessed by change from BL to Day 84 in ICSS and VR-OSDI To evaluate safety and tolerability  <u>Secondary:</u> To evaluate efficacy assessed by STT (means at Days 14 and 84) and total OSDI score (mean changes from BL to Days 14 and 84)	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)
<b>Study 1118-DRY-300</b> (SPD606-302; OPUS-2)  Safety and Efficacy	<u>Primary:</u> To evaluate efficacy assessed by change from BL to Day 84 in ICSS and EDS To evaluate safety and tolerability  <u>Secondary:</u> To evaluate efficacy assessed by change from BL to Day 84 in total corneal staining score, nasal conjunctival lissamine green staining score, eye discomfort score, and ODS	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 Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Safety</b>					
<b>Study 1118-DRY-400</b> (SPD606-303; SONATA)  Safety	<u>Primary:</u> To evaluate safety as assessed by ocular and non-ocular adverse events  <u>Secondary:</u> To evaluate safety and tolerability	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
<b>Study 1118-ACJ-100</b>  (Phase 2 allergic conjunctivitis study)	<u>Primary:</u> To evaluate safety as assessed by signs and symptoms of allergic conjunctivitis  <u>Secondary:</u> To evaluate safety and tolerability	Phase 2, single center, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 0.1, 1.0, or 5% or vehicle ophthalmic solution  60 subjects with dry eye disease (31 males/ 29 females)	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

**Reviewer’s Comment:** *The reference product will be referred to as ‘vehicle’ throughout this review since this term more accurately describes its composition than ‘placebo’.*

*Reference is made to the original submission of NDA 208-073 for Xiidra (lifitegrast ophthalmic solution) 5.0% for the treatment of dry eye disease which contained data for the following clinical dry eye studies: Phase 2 Dry Eye Study (1118-KCS-100), two Phase 3 Dry Eye Studies [1118-KCS-200 (OPUS-1) and 1118-DRY-300 (OPUS-2)] and a longer term safety study (1118-DRY-400; SONATA). These studies were reviewed during the previous cycle. The Medical Officer’s review for this submission was finalized on August 12, 2015.*

*The application received a Complete Response letter dated October 16, 2015. While the original application demonstrated safety for the treatment of dry eye disease; substantial evidence of efficacy had not been provided in the NDA. This Resubmission after*

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*Complete Response includes the requested additional clinical study, SHP606-304 (OPUS-3), intended to demonstrate efficacy when taken with the previously reviewed clinical studies.*

## 5.2 Review Strategy

*The submitted clinical study reports, clinical protocols and relevant literature reports were reviewed. Relevant portions of Modules 1, 2 and 5 of the submission were reviewed in depth.*

## 5.3 Discussion of Individual Studies/Clinical Trials

*Reference is made to the original submission of NDA 208-073 for Xiidra (lifitegrast ophthalmic solution) 5.0% for the treatment of dry eye disease which contained data for the following clinical dry eye studies: Phase 2 Dry Eye Study (1118-KCS-100), two Phase 3 Dry Eye Studies [1118-KCS-200 (OPUS-1) and 1118-DRY-300 (OPUS-2)] and a longer term safety study [1118-DRY-400( SONATA)]. These studies were reviewed during the previous cycle. For further details refer to the Medical Officer’s review finalized on August 12, 2015.*

*The application received a Complete Response letter dated October 16, 2015, because substantial evidence of efficacy had not been provided in the NDA. This Resubmission after Complete Response includes the requested additional clinical study, SHP606-304 (OPUS-3), which is the subject of this review.*

### **OPUS-3 Study (SHP606-304): A Phase 3, Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy and Safety of a 5% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Disease and History of Recent Artificial Tear Use**

#### **Study Centers**

This study was performed at forty-two investigational centers within the U. S.

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
01	12	Joseph Tauber, MD	Tauber Eye Center 4400 Broadway, Ste. 202 Kansas City, MO 64111
02	59	David Wirta, MD	Eye Research Foundation 520 Superior Ave., Ste 235 Newport Beach, CA 92663
03	14	Da-Thuy Van, MD	Houston Eye Associates 1100 Gulf Freeway, Ste. 114 League City, TX 77573
04	27	Robert Smyth-Medina, MD	North Valley Eye Medical Group, Inc. 11550 Indian Hill Rd., Ste. 341 Mission Hills, CA 91345

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<b>Site No.</b>	<b>No. of Randomized Subjects</b>	<b>Principal Investigator</b>	<b>Site Name and Address</b>
05	60	Joseph Martel, MD	Martel Eye Medical Group 11216 Trinity River Dr. Rancho Cordova, CA 95670
06	3	Michael Korenfeld, MD	Comprehensive Eye Care, Ltd. 901 E. Third Street Washington, MO 63090
07	9	Kathryn Richdale, MD	Clinical Vision Research Center 33 W. 42 <sup>nd</sup> Street New York, NY 10036
09	18	Steven Wilson, MD	John-Kenyon American Eye Institute 19 State Street New Albany, IN 47150
10	19	Parag Majmudar, MD	Chicago Cornea Consultants, Ltd. 1585 N. Barrington Rd., Ste. 502 Hoffman Estates, IL 60169
11	29	Marc Abrams, MD	Abrams Eye Center 2322 East 22 <sup>nd</sup> St., Suite 102 Cleveland, OH 44115
12	27	Kenneth Sall, MD	Sall Research Medical Center 11423 187 <sup>th</sup> St., Ste. 200 Artesia, CA 90701
13	6	Jodi Luchs, MD	South Shore Eye Care, LLP. 2185 Wantagh Ave. Wantagh, NY 11793
14	4	Mujtaba Qazi, MD	Lifelong Vision Foundation 1815 Clarkson Rd. Chesterfield, MO 63017
15	19	Kathleen Kelley, MD	Price Vision Group 9002 N. Meridian Street, Ste. 100 Indianapolis, IN 46260
16	19	Jeffrey Whitsett, MD	Whitsett Vision Group 1237 Campbell Rd. Houston, TX 77055

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<b>Site No.</b>	<b>No. of Randomized Subjects</b>	<b>Principal Investigator</b>	<b>Site Name and Address</b>
17	0	Eric Donnenfeld, MD	Ophthalmic Consultants of Long Island 200 North Village Ave., Suite 402 Rockville Centre, NY 11570
18	20	Robert Rice, MD	Rand R Eye Research, LLC 5430 Fredericksburg Rd., Ste. 100 San Antonio, TX 78229
19	0	Elizabeth Sharpe, MD	Glaucoma Consultants and Center for Eye Research, PA 721 Long Point Rd., Ste.407 Mt. Pleasant, SC 29464
20	15	Jessica Mathew, MD	University of Houston College of Optometry 4901 Calhoun Rd. 505 J Davis Armistead Bldg Houston, TX 77204
21	7	Jeffrey Lozier, MD	Arch Health Partners 15611 Pomerado Rd., 4 <sup>th</sup> Floor Poway, CA 92064
22	11	Melissa Toyos, MD	Toyos Clinic 2201 Crestmoor Rd. Nashville, TN 37215
23	1	Cynthia Matossian, MD	Matossian Eye Associates 501 Hyde Park Doylestown, PA 18902
24	16	Paul Karpecki, MD	Koffler Vision Group 120 N. Eagle Creek Drive Lexington, KY 40509
25	36	John Meyer, MD	The Eye Care Institute 1536 Story Ave. Louisville, KY 40206
26	16	Michael Depenbusch, MD	Arizona Eye Center 604 W. Warner Rd., Ste. B-6 Chandler, AZ 85225
27	0	David Evans, MD	Total Eye Care, PA 6060 Primacy Pkwy, Ste. 200 Memphis, TN 38119

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<b>Site No.</b>	<b>No. of Randomized Subjects</b>	<b>Principal Investigator</b>	<b>Site Name and Address</b>
28	25	William Lipsky, MD	Advanced Laser Vision & Surgical Institute 11550 Fuqua Street, Ste. 250 Houston, TX 77034
30	2	Rajesh Rajpal, MD	See Clearly Vision 8138 Watson Street McLean, VA 22102
31	12	Barry Katzman, MD	West Coast Eye Care Associates 6945 El Cajoh Blvd San Diego, CA 92115
32	15	Jack Abrams, MD	Abrams Eye Institute 6450 Medical Center St., Ste. 100 Las Vegas, NV 89148
33	23	Jack Greiner, OD	Clinical Eye Research of Boston 955 Main St., Ste. 307 Winchester, MA 01890
35	22	Daniel Zimmer, MD	Scott & Christie and Associates, PC 105 Brandt Dr., Ste. 201 Cranberry Township, PA 16066
36	5	Kelly Nichols, MD	University of Alabama at Birmingham 1716 University Blvd., HBP 112 Birmingham, AL 35294
37	9	Navin Tekwani, MD	Tekwani Vision Center 9911 Kennerly Rd., Ste. A St. Louis, MO 63128
38	33	Joseph Gira, MD	Ophthalmology Consultants Ltd. 12990 Manchester Rd., Ste. 201 St. Louis, MO 63131
39	18	Reginald Sampson, MD	Montebello Medical Eye Center, Inc. 229 Beverly Blvd., Montebello, CA 90640
40	2	Edward Holland, MD	Cincinnati Eye Institute 580 South Loop Rd., Suite 200 Edgewood, KY 41017
41	22	James Peace, MD	United Medical Research Institute 431-433 N. Prairie Ave. Inglewood, CA 90301

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
42	18	Jay Rubin, MD	Eye Clinics of South Texas, PA 999 E. Basse Rd., Ste. 128-B San Antonio, TX 78209
43	30	Mitchell Jackson, MD	Jackson Eye 300 N. Milwaukee Ave., Ste. L Lake Villa, IL 60046
44	2	Bruce Silverstein, MD	Shasta Eye Medical Group, Inc. 900 Butte Street Redding, CA 96001
45	19	Louis Alpern, MD	The Cataract & Glaucoma Center 4171 N. Mesa Bldg. D, Suite 100 El Paso, TX 79902
46	7	Kent Wellish, MD	Wellish Eye Institute 2110 E. Flamingo Rd., Ste. 120 Las Vegas, NV 89119

Source: Module 5.3.5.1\SHp606-304\ Section 16.1.4

### Study Objectives

#### Primary:

To evaluate the efficacy of lifitegrast compared to vehicle in improvement of symptoms of DED as measured by the mean change from baseline to Day 84 in the EDS (0-100 point visual analogue scale [VAS], both eyes)

#### Key Secondary:

To evaluate the efficacy of lifitegrast compared to placebo in improvement of symptoms of dry eye disease as measured by:

- Mean change from baseline to Day 42 in the EDS (0-100 point VAS, both eyes)
- Mean change from baseline to Day 14 in the EDS (0-100 point VAS, both eyes)

#### Secondary Objectives:

- To evaluate the efficacy of lifitegrast compared to placebo in improvement of symptoms of DED as measured by:
  - Mean change from baseline to each visit in the 6 additional items of the 7-item VAS (0-100 point scale, both eyes)
  - Mean change from baseline to each visit in the designated study eye in the ocular discomfort score (ODS; 0-4 point scale)
- To evaluate the safety and tolerability of lifitegrast compared to placebo

### Methodology

This was a Phase 3, multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel arm study conducted in the US to evaluate the efficacy and safety of lifitegrast ophthalmic solution (5.0%) (hereafter referred to as lifitegrast) administered twice daily in each eye for 12 weeks. The study was conducted in adult male and female subjects with DED and a history of artificial tear use within 30 days of screening (but not during the 72 hours prior to Visit 1).

Approximately 700 subjects were planned to be randomized 1:1 (approximately 350 per treatment arm) to receive either lifitegrast or vehicle. Randomization was stratified by inferior corneal fluorescein staining score ( $\leq 1.5$  or  $>1.5$ ) and EDS ( $<60$  or  $\geq 60$ ) at baseline. The study eye was determined based on inferior corneal fluorescein staining score and STT. Eligible subjects had a positive response in at least 1 eye. A positive response in at least 1 eye was defined as meeting ALL of the following criteria in the same eye at both Day -14/Visit 1 and Day 0 /Visit 2:

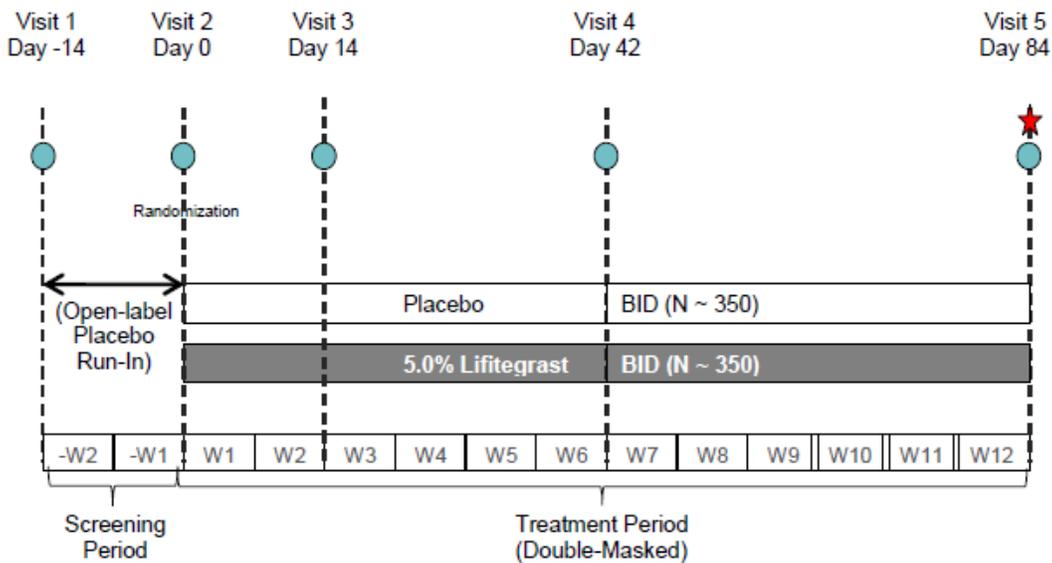
- Inferior corneal fluorescein staining score  $\geq 0.5$
- Schirmer tear test  $\geq 1$  and  $\leq 10$  mm.

If both eyes met both criteria, the eye with the greater score in inferior corneal fluorescein staining at Visit 2 was selected as the study eye. If both eyes had equal scores in staining at Day 0 / Visit 2, then the eye with the lowest STT value at Day 0 / Visit 2 was designated as the study eye. If both eyes had equal inferior corneal fluorescein staining and STT scores at Day 0 /Visit 2, the right eye was selected as the study eye.

Approximately 1400 subjects were planned to be screened to ensure 700 randomized subjects.

Subjects who signed informed consent began the screening period. Any subject who was currently taking a prohibited treatment began a prespecified washout period. Upon completion of the washout period (if necessary), subjects were screened at Visit 1 (Screening Visit). Subjects who met eligibility criteria at the end of the screening visit (Visit 1) began a standard regimen of open-label vehicle for a minimum of 11 days to assess compliance with twice daily medication administration. Subjects returned for the baseline visit (Visit 2) to confirm eligibility. Subjects who continued to meet all eligibility criteria were randomized and evaluated for efficacy and safety at Weeks 2, 6, and 12 (Visits 3-5).

### Study Design Schematic



BID=twice daily; W=week

Source: CSR Module 5.3.5.1\SHP606-304\Section 3.1

## Study Population

### Inclusion Criteria

Subjects were not considered eligible for the study without meeting all of the following criteria:

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study
3. At 18 years of age at the time of screening
4. Male or nonpregnant female (confirmed by negative urine pregnancy test for all females nonlactating female who agreed to comply with any applicable contraceptive requirements of the protocol, or females of nonchildbearing potential)
5. As needed or scheduled use of nonprescription (over-the-counter) artificial tear substitute for symptoms of DED within 30 days prior to the screening visit (Visit 1) and willingness to suspend use of tear substitutes 72 hours prior to the screening visit and for the duration of study participation
6. Best corrected visual acuity (BCVA) of 0.7 logMAR or better (logMAR < 0.7; Snellen equivalent score of 20/100 or better) in each eye at the screening visit (Visit 1)
7. Subject-reported history of DED in both eyes
8. Corneal fluorescein staining score  $\geq 2$  (0-4 point scale) in at least 1 region in at least 1 eye at Visits 1 and 2
9. Conjunctival redness score  $\geq 1$  (0-4 point scale with allowance for 0.5 point increments) in at least 1 eye at Visits 1 and 2
10. Eye dryness score  $\geq 40$  (0-100 point VAS, both eyes) at Visits 1 and 2
11. A positive response in at least 1 eye, defined as meeting ALL of the following criteria in

the same eye at both Visits 1 and 2:

- a. Inferior corneal fluorescein staining score  $\geq 0.5$  (0-4 scale with allowance for 0.5 point increments)
- b. Schirmer tear test (STT; without anesthesia)  $\geq 1$  and  $\leq 10$  mm

### **Exclusion Criteria**

Subjects were excluded from the study if any of the following exclusion criteria were met:

1. Known hypersensitivity to investigational product or its components
2. Prior randomization in a lifitegrast (SHP606, SPD606, SAR 1118) clinical study
3. Subjects who were employees or immediate family members of employees at the investigational site
4. Subjects who were members of the same household
5. Subjects with DED secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or destruction of conjunctival goblet cells (as with vitamin A deficiency). Subjects with incidental scars secondary to refractory surgery (i.e., LASIK surgery) that in the opinion of the principal investigator would not have interfered with study compliance and/or outcome measures were not excluded from the study
6. Any ocular condition that, in the opinion of the investigator, could have affected study parameters including, but not limited to, lid margin disorders (e.g., blepharitis including staphylococcal, demodex, or seborrheic; meibomian gland disease, excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, tinea versicolor, and/or active ocular inflammation
7. Currently active or history of ocular herpes or any other ocular infection within 30 days of the screening visit (Visit 1)
8. Any known history of immunodeficiency disorder, human immunodeficiency virus, hepatitis B or C, or evidence of acute active hepatitis A (antihepatitis A virus immunoglobulin M), or organ or bone marrow transplant
9. Any other significant illness that, in the opinion of the investigator, could have interfered with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes.
10. Subjects with secondary Sjogren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosus) were eligible provided the subject met all other inclusion and exclusion criteria AND were not in a medical state that, in the opinion of the investigator, could have interfered with study parameters; were not taking systemic/ocular steroids; and were not immunodeficient/immunosuppressed (e.g., receiving immunosuppressive drugs to manage their baseline medical state)
11. Any known history of alcohol and/or drug abuse within 12 months prior to the screening visit (Visit 1) that, in the opinion of the investigator, may have interfered with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject
12. Positive urine pregnancy test or nursing an infant (female subjects only)
13. Any blood donation or significant loss of blood within 56 days of the screening visit

- (Visit 1) or during the study
14. Use of any topical medication and/or antibiotic for the treatment of blepharitis or meibomian gland disease during the study
  15. Use of any investigational product or device within 30 days prior to the screening visit (Visit 1) or during the study
  16. Use of the following medications (topical, topical ophthalmic, systemic, and/or injectable) within the time associated washout restrictions below or during the study:
    - a. Topical cyclosporine: within 6 weeks prior to administration of open-label placebo run-in
    - b. Any medication (oral or topical) known to cause ocular drying: within 30 days of administration of open-label placebo run-in unless the subject had been receiving a stable dose over the past 30 days with no change in dose anticipated during the study period
    - c. Oral aspirin or aspirin-containing products: within 30 days of administration of open-label placebo run-in unless the subject had been receiving a stable dose over the past 30 days with no change in dose anticipated during the study period
    - d. Corticosteroids or mast cell stabilizers (including ocular): within 14 days prior to the administration of open-label placebo run-in
    - e. Antihistamines (including ocular): within 72 hours prior to administration of open-label placebo run-in and throughout the subject's participation during the study
    - f. All other topical ophthalmic preparations (including artificial tear substitutes): within 72 hours prior to administration of open-label placebo run-in
    - g. Punctal occlusion:
      - i. Punctal cauterization: Administration of open-label placebo run-in may not have occurred until 12 weeks following the procedure.
      - ii. Permanent/semi-punctal plugs: Administration of open-label placebo run-in may not have occurred until 12 weeks following the procedure. If punctal plug fell out during the study, it should have been reinserted.
      - iii. Temporary punctal plugs: Not permitted. If subject had a history of use of temporary punctal plugs, administration of open-label placebo run-in may not have occurred until 12 weeks since last insertion and puncta are plug-free, as determined by the investigator.
  17. Unwilling to avoid wearing contact lenses during the study
  18. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any planned ocular surgical procedure during the study period
  19. History of yttrium aluminum garnet-laser posterior capsulotomy in past 6 months prior to Visit 1
  20. Non-compliance (<80% or >120%) with placebo regimen during the run-in period
  21. Missing or unaccounted for (b) (4) during the run-in period
  22. Less than 11 consecutive days of vehicle administration during the run-in period

### **Removal of Subjects**

Subjects (or their legally authorized representative) had the right to withdraw consent for participation in the study at any time without prejudice. The investigator was to withdraw any subject who requested to be withdrawn from the study. A subject's participation in the study could have been discontinued at any time at the discretion of the investigator and/or sponsor and in accordance with his/her clinical judgment. However, investigators were encouraged to contact the sponsor, when possible, to discuss possible reasons for discontinuation prior to withdrawing a subject from the study. When possible, the tests and evaluations listed for the Early Termination Visit were carried out.

The sponsor reserved the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual investigator or site for poor enrollment or non-compliance.

Reasons for which the investigator or sponsor could have withdrawn a subject from the study included, but were not limited to, the following:

- Subject experienced a serious or intolerable AE
- Subject required medication prohibited by the protocol
- Subject did not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or did not meet entry criteria
- Subject was lost to follow-up
- Subject became pregnant.

If a subject failed to return for scheduled visits, documented efforts were made to determine the reason. If the subject could not be reached by telephone after 2 attempts, a certified letter was sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the investigator. Randomized subjects that were discontinued from the study were not replaced.

### **Identity of Investigational and Reference Products**

Investigational product was supplied as a sterile, clear, liquid solution containing 5% lifitegrast concentration in 5 (b) (4) single-dose, (b) (4) low-density polyethylene unit dose (b) (4) with a fill volume of approximately 0.2 mL. Each mL of a 5% solution contained 50 mg of lifitegrast active pharmaceutical ingredient. In addition to lifitegrast, the components of the solution were: (b) (4). The lifitegrast batch numbers were 4E16-2 and 4E17-2.

The vehicle consisted of all components of the investigational product solution with the exception of lifitegrast. The batch number was 4E15.

### **Criteria for Evaluation**

The following efficacy assessments were performed at every study visit:

- VAS (burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, and pain)
- ODS

The following safety assessments were also performed at the study visit indicated:

- Adverse events (ocular and non-ocular); all study visits
- Conjunctival redness: all study visits
- Corneal fluorescein staining (superior, central, and inferior regions); all study visits
- Conjunctival staining with lissamine green (temporal and nasal regions): all study visits
- Schirmer tear test: all study visits
- Drop comfort: Day 0/Visit 2, Day 14/Visit 3, Day 42/Visit 4, and Day 84/Visit 5
- Best corrected visual acuity: all study visits
- Slit lamp biomicroscopy: all study visits
- Dilated funduscopy: Day -14/Visit 1 and Day 84/Visit 5
- Pregnancy test: Day -14/Visit 1, Day 0/Visit 2, and Day 84/Visit 5

Additionally, a health economics and outcomes research assessment was conducted: The EuroQol-5 Dimension 5-level Questionnaire was administered to subjects just before randomization at Day 0/Visit 2 and after completion of all other assessments at Day 84/Visit 5.

### **Analysis Populations**

**Randomized Population:** All randomized subjects for whom a randomization number was assigned.

**Safety Population:** All randomized subjects who received at least 1 dose of investigational product.

**ITT Population:** All randomized subjects who took at least 1 dose of investigational product.

### **Determination of Sample Size**

A sample size of 350 subjects per treatment group (700 subjects) ensured more than 90% power to detect a difference of 10.0 units (with SD of 36.0) in mean change from baseline to Day 84 in EDS between lifitegrast and placebo at a 2-sided 5.0% type I error. The sample size of 350 subjects per treatment group also ensured more than 85% power to detect a difference of 8.0 units (with SD of 34.0) in mean change from baseline to Day 42 between the treatment groups and more than 80% power to detect a difference of 6.5 units (with SD of 30.0) in mean change from baseline to Day 14 between the treatment groups. It was expected that few, if any, subjects were to be excluded from the primary efficacy analysis due to missing data given that missing efficacy assessments were imputed by last observation carried forward (LOCF).

### **Handling of Dropouts or Missing Data**

Missing post baseline efficacy assessments were imputed from post baseline values using the last observation carried forward (LOCF) method. All efficacy analyses were performed using LOCF, unless stated otherwise. If a subject had no post baseline efficacy assessment, then no LOCF was done for that efficacy assessment for the subject and, for that efficacy assessment, the subject was not included in analysis of the ITT population with LOCF.

### **Efficacy Analyses**

The primary, key secondary and secondary efficacy analyses were performed on the ITT population and presented by treatment group. The primary efficacy endpoint was defined as the mean change from baseline to Day 84 in EDS. The primary analysis was performed using a stratified 2-sample t-test (ANOVA). The stratification factors used for randomization were used for this analysis. The individual strata contributed to the overall analysis proportionate to their size. The ANOVA model used to conduct the protocol-specified primary treatment comparison included treatment, strata, and the interaction between treatment and strata. Sensitivity analyses were done on the primary efficacy endpoint using additional statistical methods, particularly, a nonparametric Wilcoxon rank sum test (LOCF) and mixed model for repeated measures ANOVA (no imputation).

The two key secondary efficacy endpoints were defined as the change from baseline to Day 42 in EDS and change from baseline to Day 14 in EDS. The two key secondary efficacy endpoints were analyzed similarly to the primary efficacy endpoint by the stratified 2-sample t-test using the ANOVA model. Using a hierarchical approach, multiplicity adjustments were done on the key secondary efficacy endpoints testing. Sensitivity analyses were done on the key secondary efficacy endpoints similar to the primary efficacy endpoint.

Other secondary efficacy endpoints were defined as the change from baseline to Days 14, 42, and 84 in the ocular discomfort score in the study eye and the items of the VAS: burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, and pain. These endpoints were analyzed similarly to the primary efficacy by the stratified 2-sample t-test using the ANOVA model. No multiplicity adjustment was done on the secondary efficacy endpoints. Summary statistics included nominal p-values were reported.

### **Safety Analyses**

Safety data were presented for the safety population by treatment group. The safety data collected at the baseline visit (Visit 2) or the last data collected prior to treatment exposure were used as the baseline value for safety analyses.

### **Interim Analysis**

For a required 4-month safety update to a New Drug Application in the US, a masked safety analysis occurred before the final database lock.

### Study Schedule

Procedure	Screening period <sup>a</sup> Visit 1 (Week -2) Days -14 to -1 (±3; up to +84)		Visit 2 Week -1 Day 0			Days 1-13	Visit 3 <sup>b</sup>	Days 15-41	Visit 4 <sup>b</sup>	Days 43-83	Visit 5 <sup>b</sup>	ET
	Pre-washout	Post-washout	Pre-randomization	Randomization	Post-randomization		Week 2 Day 14 ± 3		Week 6 Day 42 ± 3		Week 12 Day 84 ± 7	
Informed consent <sup>a</sup>	X											
Demographic data	X											
Height and weight (subject-reported)	X											
Medical history/medication history <sup>c</sup>	X	X										
Concomitant medication assessment and reporting	X	X	X	X	X		X		X		X	X
Inclusion/exclusion criteria	X	X	X									
Urine pregnancy test <sup>d</sup>		X	X								X	X
<b>Subjective measures</b>												
VAS <sup>e</sup>		X	X				X		X		X	X
ODS		X	X				X		X		X	X
Drop comfort assessment <sup>f</sup>					X		X		X		X	
EQ-5D-5L <sup>g</sup>			X								X	X
<b>Objective measures</b>												
BCVA <sup>h</sup>		X	X				X		X		X <sup>h</sup>	X <sup>h</sup>
Slit lamp biomicroscopy <sup>i</sup>		X	X				X		X		X <sup>i</sup>	X <sup>i</sup>

Procedure	Screening period <sup>a</sup> Visit 1 (Week -2) Days -14 to -1 (±3; up to +84)		Visit 2 Week -1 Day 0			Days 1-13	Visit 3 <sup>b</sup> Week 2 Day 14 ± 3	Days 15-41	Visit 4 <sup>b</sup> Week 6 Day 42 ± 3	Days 43-83	Visit 5 <sup>b</sup> Week 12 Day 84 ± 7	ET
	Pre-washout	Post-washout	Pre-randomization	Randomization	Post-randomization							
Conjunctival redness score assessment		X	X				X		X		X	X
Corneal fluorescein staining score assessment		X	X				X		X		X	X
Conjunctival staining (lissamine green)		X	X				X		X		X	X
STT (without anesthesia)		X	X				X		X		X	X
Dilated funduscopy <sup>j</sup>		X <sup>j</sup>									X <sup>j</sup>	X <sup>j</sup>
<b>Investigational product treatment</b>												
Open-label placebo administration at study site		X <sup>k</sup>	X <sup>l</sup>									
Open-label placebo dispensation		X										
Open-label placebo administration at home		X <sup>k</sup>										

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Procedure	Screening period <sup>a</sup> Visit 1 (Week -2) Days -14 to -1 (±3; up to +84)		Visit 2 Week -1 Day 0			Days 1-13	Visit 3 <sup>b</sup> Week 2 Day 14 ± 3	Days 15-41	Visit 4 <sup>b</sup> Week 6 Day 42 ± 3	Days 43-83	Visit 5 <sup>b</sup> Week 12 Day 84 ± 7	ET
	Pre-washout	Post-washout	Pre-randomization	Randomization	Post-randomization							
Open-label placebo vial collection/investigational product accountability/compliance assessed <sup>m</sup>			X									
Randomization				X								
Investigational product administration at study site					X <sup>n</sup>		X <sup>o</sup>		X <sup>o</sup>		X <sup>p</sup>	
Investigational product dispensation					X		X		X			
Investigational product administration at home						X	X	X	X	X		
Investigational product collection/investigational product accountability/compliance assessed <sup>m</sup>							X		X		X	X
AE assessment and reporting <sup>q</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Access IRT	X	X		X			X		X		X	X

Procedure	Screening period <sup>a</sup> Visit 1 (Week -2) Days -14 to -1 (±3; up to +84)		Visit 2 Week -1 Day 0			Days 1-13	Visit 3 <sup>b</sup>	Days 15-41	Visit 4 <sup>b</sup>	Days 43-83	Visit 5 <sup>b</sup>	ET
	Pre-washout	Post-washout	Pre-randomization	Randomization	Post-randomization		Week 2 Day 14 ± 3		Week 6 Day 42 ± 3		Week 12 Day 84 ± 7	
Study exit											X	X

AE=adverse event; BCVA=best corrected visual acuity; DED=dry eye disease; ET=early termination; EQ-5D-5L=EuroQol-5 Dimension 5-level Questionnaire; IRT=interactive response technology; ODS=ocular discomfort score; STT=Schirmer tear test; VAS=visual analogue scale

<sup>a</sup> Subjects signed informed consent prior to performing any study-related procedures. A washout period may have been required to discontinue any prohibited medication or treatments. A subject should not have been instructed to discontinue use of any medication or treatment to participate in this study until after informed consent was obtained. Screening assessments may have taken place across several days to allow an appropriate time frame to complete all procedures and confirm study eligibility, but placebo run-in should not have been dispensed until washout and all screening assessments required to confirm initial eligibility were complete. Subjects must have been administered placebo run-in for a minimum of 11 consecutive days immediately prior to Visit 2. Extensions to the screening window to accommodate washout timeframes from prohibited medications or treatments were not permitted beyond 98 days; some screening assessments may have needed to be repeated after washout.

<sup>b</sup> Every effort was made to schedule visits on the designated study days; however, after baseline, visits had a ±3 day visit window to allow for weekends and slight variations in subject schedules. Visits were calculated from baseline and not the prior visit.

<sup>c</sup> All ocular medical history and ocular medications/treatments used to treat DED at any time were recorded. Non-ocular medical history within 1 year of screening was recorded. Non-ocular medications/treatments and ocular medications/treatments used for conditions other than DED within 60 days prior to screening were recorded.

<sup>d</sup> For all females.

<sup>e</sup> On visits when the VAS was completed, it was completed prior to any other ophthalmologic test or assessment.

<sup>f</sup> Drop comfort assessments were obtained for each eye immediately, and 1, 2, and 3 minutes following instillation of the investigational product at the site by trained study personnel. If the score was not ≤3 at minute 3, the drop comfort assessment was repeated at minutes 5, 10, and 15 until the score was ≤3. If the score was >3 at minute 15, it was recorded as an AE.

<sup>g</sup> At Visit 2, the EQ-5D-5L was completed after all other screening assessments were completed, following open-label placebo administration and just prior to randomization. At Visit 5 and Early Termination, the EQ-5D-5L was the final assessment completed.

<sup>h</sup> A BCVA assessment was measured prior to open-label placebo or randomized investigational product administration at all visits. At Visit 5, a second BCVA assessment was measured after the final dose of investigational product was administered by site personnel. In the case where a subject was prematurely terminated after dosing, this procedure was performed.

<sup>i</sup> A slit lamp examination was performed prior to open-label placebo or randomized investigational product administration at all visits. At Visit 5, a second slit lamp examination was performed after the final dose of investigational product was administered by site personnel. In the case where a subject was prematurely terminated after dosing, this procedure was performed.

<sup>j</sup> Dilated funduscopy was performed at the end of the visit after other ophthalmic procedures/assessments were completed, but prior to administration of open-label placebo at Visit 1 or prior to EQ-5D-5L at Visit 5 or early termination.

<sup>k</sup> At the screening visit (Visit 1), following washout if applicable, for training purposes, subjects self-administered open-label placebo approximately 15 minutes following the last study assessment under the supervision of trained study personnel. Only 1 dose of open-label placebo was administered on the day of Visit 1. Subjects were instructed not to administer a second dose that day and to begin dosing the following morning. Subjects were administered placebo run-in for a minimum of 11 consecutive days immediately prior to Visit 2.

<sup>l</sup> At the baseline visit (Visit 2), trained site personnel administered the open-label placebo approximately 15 minutes following the last screening study assessment. Subjects were instructed not to administer a dose of open-label placebo at home prior to the visit. Subjects who had a positive response and who continued to meet all other eligibility criteria were randomized.

<sup>m</sup> Returned open-label placebo/investigational product was reviewed and assessed for compliance and confirmation that all ampules were returned prior to dispensation of additional investigational product. Compliance issues were discussed with subjects. Site personnel confirmed that subjects had not administered the morning dose prior to the office visit.

<sup>n</sup> For randomized subjects, trained site personnel administered the first dose of randomized investigational product approximately 15 minutes following the instillation of the open-label placebo drops. Only 1 dose of randomized investigational product was administered on the day of the baseline visit (Visit 2). Subjects were instructed not to administer a second dose that day and to begin randomized dosing the following morning.

<sup>o</sup> At Visits 3-4, trained site personnel administered the dose of randomized investigational product approximately 15 minutes following the last study assessment (except for the drop comfort assessments). This was the first dose of the day for the subject. Subjects were instructed not to administer a dose of investigational product at home on days of office visits prior to the visit. Subjects were instructed to self-administer the second dose of the day in the evening prior to bedtime.

<sup>p</sup> At Visit 5, trained site personnel administered the dose of randomized investigational product approximately 15 minutes following the last study assessment (except for the drop comfort assessments). This was the first dose of the day for the subject. Subjects were instructed not to administer a dose of investigational product at home prior to the visit. Only 1 dose of investigational product was administered on the day of Visit 5.

<sup>q</sup> Adverse events were collected beginning from the signing of informed consent. All AEs were followed to closure (the subject's health returned to his/her baseline status or all variables returned to normal), regardless of whether the subject was still participating in the study. Closure indicated that an outcome was reached, stabilization was achieved (the investigator did not expect any further improvement or worsening of the event), or the event was otherwise explained.

**Reviewer's Comment:**

*Acceptable.*

### **Changes in Study Conduct**

The original protocol (Version 1.0, dated July 29, 2014) was amended twice.

#### Protocol Amendment 1 (dated 22 Dec 2014)

- Increased the number of sites to approximately 35 to mitigate against delayed study start
- Added the definition of “study eye” to be consistent with the prior protocols
- Clarified the exclusion criteria language to exclude immediate family members of site employees from participation
- Clarified the exclusion criteria language to specify that prior participation is prior randomization in a lifitegrast study
- Clarified the use of prior/concomitant punctal plugs/occlusion and the time-associated restrictions
- Provided overall clarification on the screening period, including procedures, washout timeframes, and minimum number of run-in days
- Updated the schedule of assessments to ensure the requirements for EQ-5D-5L were consistent throughout the protocol
- Clarified the withdrawal criteria
- Clarified the order of assessments at each visit

#### Protocol Amendment 2 (dated 14 May 2015)

- Increased the number of sites to approximately 40 to mitigate against delayed study start
- Updated the schedule of assessments to ensure the requirements for the placebo run-in were consistent throughout the protocol
- Clarified that all AEs must have been followed to closure
- Updated the schedule of assessments to ensure the requirements for dilated funduscopy were consistent throughout the protocol
- Clarified the visits requiring a urine pregnancy test
- Clarified that the investigator may have used his/her discretion to determine whether slit lamp biomicroscopy changes that were considered not clinically significant or DED progression should have been considered AEs

### **Changes in the Planned Analyses**

There were no changes to the planned analyses.

## 6 Review of Efficacy – Dry Eye Indication

### Efficacy Summary

#### 6.1 OPUS-3 (Study SHP606-304)

For the treatment of the signs and symptoms of dry eye disease.

##### 6.1.1 Methods

The description of the clinical trial design is contained in Section 5.3. Clinical study reports, clinical protocols and literature references were submitted related to the clinical trial in support of the New Drug Application.

##### 6.1.2 Demographics

**Table 6.1.2-1  
Demographic Characteristics – Randomized Population**

Variables		Vehicle N=356	5% LIF N=355
Age (years)	Mean (SD)	58.6 (14.84)	58.8 (14.10)
	≥ 65 years, n (%)	137 (38.5)	128 (36.1)
	≥ 75 years, n (%)	44 (12.4)	48 (13.59)
Sex: n (%)	Male	87 (24.4)	87 (24.5)
	Female	269 (75.6)	268 (75.5)
Race: n (%)	White	279 (78.4)	265 (74.6)
	Black or African American	47 (13.2)	48 (13.5)
	Asian	24 (6.7)	24 (6.8)
	American Indian or Alaska Native	0	2 (0.6)
	Native Hawaiian or other Pacific Islander	1 (0.3)	2 (0.6)
	Other	5 (1.4)	14 (3.9)
Ethnicity: n (%)	Hispanic or Latino	58 (16.3)	60 (16.9)
	Not Hispanic or Latino	298 (83.7)	295 (83.1)
Source: CSR, Section 8.2, Table 5			

**Reviewer’s Comment:**

*Patient demographics were well-balanced across the treatment groups at baseline.*

**Table 6.1.2-2  
Randomization Strata – Randomized Population**

	<b>Vehicle N=356 n (%)</b>	<b>5% LIF N=355 n (%)</b>
Inferior corneal staining score ≤ 1.5, eye dryness score < 60	20 (5.6)	19 (5.4)
Inferior corneal staining score ≤ 1.5, eye dryness score ≥ 60	33 (9.3)	32 (9.0)
Inferior corneal staining score >1.5, eye dryness score < 60	108 (30.3)	109 (30.7)
Inferior corneal staining score > 1.5, eye dryness score ≥ 60	195 (54.8)	195 (54.9)
Source: CSR, Section 8, Table 6		

Note: A small percentage of subjects were incorrectly stratified at randomization.

**Reviewer’s Comment:**

*The treatment groups were well balanced with regard to the randomization strata at baseline. The majority of subjects had an inferior corneal staining score > 1.5 and eye dryness score ≥ 60.*

**Prior and Concomitant Medications**

Overall, almost all subjects took a prior ocular medication because subjects were required to use artificial tears within 30 days of screening. One subject, 18-010, did not meet this requirement. Overall, 2.4% of subjects took concomitant medications for ocular health. The most common concomitant medication for ocular health was Tears Plus (0.4%). Overall, 16.6% of subjects took prior non-ocular medications. Most subjects (78.9%) took concomitant non-ocular medications. The most common concomitant non-ocular medications (>10%) were acetylsalicylic acid, viterra (vitamins), cholecalciferol, and lisinopril.

**Reviewer’s Comment:**

*Unlike the Phase 2 Dry Eye study and OPUS-1, artificial tear use within 30 days of Visit 1 was required for study entry.*

**6.1.3 Subject Disposition**

A total of 1542 subjects were screened, and 558 subjects did not enter the Vehicle Run-in Period due to screening failure. A further 273 subjects were not randomized after the Vehicle Run-in Period due to screening failure. Of the 711 randomized subjects (vehicle: 356 subjects; lifitegrast: 355 subjects). The ITT population and Safety Populations included all unique randomized subjects who received at least one dose of investigational product. The ITT population was based upon the treatment assigned while the safety population was based upon the treatment received. Two subjects (Subject 01-011 and Subject 38-013) were randomized to vehicle but incorrectly received lifitegrast in Visit 2. These subjects were included in the

lifitegrast group for the safety population, but in the vehicle group for the randomized and ITT populations.

**Table 6.1.3-1  
Subject Disposition**

	<b>Vehicle N=356 n (%)</b>	<b>5% LIF N=355 n (%)</b>	<b>Total N=711 n (%)</b>
Screened subjects <sup>a</sup>			1542
Number of subjects not starting Vehicle Run-in Period			558
Number of subjects not randomized after Vehicle Run-in Period			273
Number of subjects randomized			711
Randomized without vehicle run-in <sup>c</sup>	1	1	2
Included in data analysis			711
Randomized subjects	356	355	711
Safety Population <sup>b</sup>	354 (99.4)	357 (100.6)	711 (100.0)
ITT Population	356 (100.0)	355 (100.0)	711 (100.0)
Completed Study	318 (89.3)	319 (89.9)	637 (89.6)
Withdrew from Study	38 (10.7)	36 (10.1)	74 (10.4)
<i>Reasons for Withdrawal</i>			
Adverse event	9 (2.5)	22 (6.2)	31 (4.4)
Lost to follow-up	4 (1.1)	2 (0.6)	6 (0.8)
Non-compliance	5 (1.4)	2 (0.6)	7 (1.0)
Erroneously admitted	7 (2.0)	4 (1.1)	11 (1.5)
Other	13 (3.7)	6 (1.7)	19 (2.7)
Source: CSR Section 8.1, Table 4			

Note: Percentages based on Randomized Population.

a Number may reflect multiple screenings for the same person

b Subjects are categorized by actual treatment received, even if randomized to the other treatment. Subject 01-011 and 38-013 were randomized to the vehicle group, but received lifitegrast via an incorrect kit at Visit 2. These subjects were included in the lifitegrast group for the Safety Population, but in the vehicle group for the Randomized and ITT populations.

c Two randomized subjects 03-017 and 44-012 were incorrectly dispensed investigational drug at Visit 1 instead of placebo run-in kit, hence did not go through the run-in period. Both subjects were withdrawn by the Sponsor.

**Reviewer's Comment:**

*The subject completion rate was 90% in the vehicle and lifitegrast groups. The most frequent reason for discontinuation in the lifitegrast group was adverse event which was experienced by 6% of subjects in the lifitegrast group and 3% in the vehicle group.*

**Table 6.1.3-2 Subjects Discontinued from Treatment or Study  
Safety Population**

<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
AE – Accelerated hypertension	Vehicle	41-004	42
AE – Basal cell carcinoma; RTX	Vehicle	32-039	35
AE – Blurred vision	Lifitegrast	02-048	23
AE – Blurred vision	Vehicle	02-045	21
AE – Blurred vision; burning upon instillation; SPK; conjunctival injection	Lifitegrast	46-002	7
AE – Blurry vision	Lifitegrast	37-019	3
AE – Blurry vision after instillation	Lifitegrast	35-024	42
AE – Burning and tearing	Lifitegrast	13-014	2
AE – Burning upon instillation past 15 min; diarrhea	Lifitegrast	42-002	54
AE – Burning, headaches, eyelid erythema and conjunctival injection	Lifitegrast	04-027	31
AE – Conjunctival hyperemia	Lifitegrast	41-001	2
AE – Corneal infiltrate	Vehicle	24-011	16
AE – Decreased VA, photophobia, burning, corneal edema	Lifitegrast	20-005	15
AE – Dysgeusia, sinus pressure, headache	Lifitegrast	25-008	5
AE – Eye irritation OU	Lifitegrast	05-088	42
AE – Fractured legs	Vehicle	43-008	9
AE – HSV keratitis	Vehicle	11-003	31
AE – Intense itching, epiphora, redness	Lifitegrast	09-027	12
AE – Lung cancer	Lifitegrast	04-032	76
AE – Ocular burning	Lifitegrast	02-010	23
AE – Ocular discomfort	Vehicle	02-086	7
AE – Ocular discomfort upon instillation	Lifitegrast	02-016	21
AE – Pain upon instillation	Lifitegrast	18-010	16
AE – Photophobia, pain, blurred vision	Lifitegrast	10-015	7
AE – Pneumonia	Lifitegrast	33-023	81
AE – Recurrent erosion	Vehicle	13-016	66
AE – Redness, decrease in BCVA, and irritation	Lifitegrast	03-021	41
AE – Squamous cell carcinoma	Lifitegrast	32-027	16
AE – Stinging	Lifitegrast	41-033	6
AE – Stroke	Lifitegrast	43-045	70
AE – Worsening dry eye	Vehicle	46-005	14
Lost to follow-up	Lifitegrast	05-035	43
Lost to follow-up	Lifitegrast	20-025	1

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<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
Lost to follow-up	Vehicle	03-015	15
Lost to follow-up	Vehicle	04-004	14
Lost to follow-up	Vehicle	12-053	42
Lost to follow-up	Vehicle	18-001	43
Noncompliance	Lifitegrast	20-019	154
Noncompliance	Lifitegrast	20-036	41
Noncompliance	Lifitegrast	38-007	50
Noncompliance	Vehicle	02-052	74
Noncompliance	Vehicle	03-023	45
Noncompliance	Vehicle	05-033	86
Noncompliance	Vehicle	05-061	83
Noncompliance	Vehicle	38-030	43
Other – Erroneously admitted	Lifitegrast	23-006	42
Other – Erroneously admitted	Lifitegrast	35-021	47
Other – Erroneously admitted	Lifitegrast	36-005	8
Other – Erroneously admitted	Lifitegrast	44-012	12
Other – Erroneously admitted	Vehicle	03-017	14
Other – Erroneously admitted	Vehicle	05-014	7
Other – Erroneously admitted	Vehicle	22-024	14
Other – Erroneously admitted	Vehicle	32-012	11
Other – Erroneously admitted	Vehicle	33-026	23
Other – Erroneously admitted	Vehicle	39-013	84
Other – Erroneously admitted	Vehicle	46-007	84
Other – Family emergency	Lifitegrast	02-046	18
Other – Family emergency	Lifitegrast	12-028	59
Other – Lack of efficacy; withdrew consent	Vehicle	25-065	29
Other – Lack of efficacy	Lifitegrast	26-040	41
Other – Moving out of state	Lifitegrast	11-032	42
Other – Protocol deviation	Vehicle	32-013	76
Other – Protocol deviation; corticosteroid use during study	Vehicle	26-007	84
Other – Protocol violation	Lifitegrast	04-012	42
Other – Protocol violation (Started taking Prednisone)	Vehicle	05-003	15
Other – Subject moving	Vehicle	11-013	22
Other – Subject moving	Vehicle	33-014	36
Other – Subject withdrew consent	Vehicle	28-011	1
Other – Took an excluded medication; Early termination per sponsor request	Vehicle	02-031	43

Reason for Discontinuation	Treatment	Subject Number	Study Duration
Other – Withdrew consent	Lifitegrast	01-023	43
Other – Withdrew consent	Vehicle	12-064	22
Other – Withdrew consent	Vehicle	38-033	21
Other – Withdrew consent	Vehicle	38-054	63
Other – Withdrew consent	Vehicle	44-007	89

Source: Study SHP606-304; CSR, Section 16.2.1

**Reviewer’s Comment:**

*The most frequent reasons for discontinuation were adverse reactions related to instillation site reaction and instillation site irritation in the lifitegrast group.*

**Protocol Deviations**

During a masked review of the data prior to database lock and unmasking, the applicant reviewed the protocol deviations captured on the eCRF. Most of the reported deviations were determined to be minor, i.e., not affecting the efficacy or safety assessments of study subjects.

The following categories of deviations were determined to be important with the potential to affect the efficacy or safety assessments.

- Overall treatment compliance outside the protocol-specified range: A total of 28 (2.9%) subjects (vehicle, 4.2%; lifitegrast, 3.6%) had an overall treatment compliance <80% or >120%.
- Incorrect stratification of subjects during randomization: Some subjects were assigned to the incorrect strata at randomization. A sensitivity analysis using the corrected strata was performed and demonstrated no impact of incorrect stratification on the efficacy analyses.

**Table 6.1.3-3  
Randomization to Incorrect Strata  
(Randomized Population)**

	Randomization Strata	Value at Randomization	Vehicle N=356 n (%)	5% LIF N=355 n (%)
Inferior corneal staining score	≤ 1.5	> 1.5	16 (4.5)	20 (5.6)
	> 1.5	≤ 1.5	9 (2.5)	6 (1.7)
Eye dryness	< 60	≥ 60	6 (1.7)	8 (2.3)
	≥ 60	< 60	7 (2.0)	5 (1.4)
Source: CSR, Section 8.5, Table 8				

Note: A small percentage of subjects were incorrectly stratified at randomization.

- Used prohibited medication: Overall, 3.5% of subjects (vehicle, 3.1%; lifitegrast, 3.9%) used a prohibited concomitant medication during the study.

- Failure to meet inclusion/exclusion criteria: A total of 23 subjects (3.2%) (10 subjects vehicle; 13 subjects lifitegrast) were randomized in the study, but did not meet all inclusion/exclusion criteria.

Subjects 01-011 and 38-013 were randomized to vehicle but incorrectly received lifitegrast at Day 0/ Visit 2. These subjects were included in the lifitegrast group of the safety population and in the vehicle groups of the randomized and ITT populations.

#### 6.1.4 Analysis of Primary Endpoint(s)

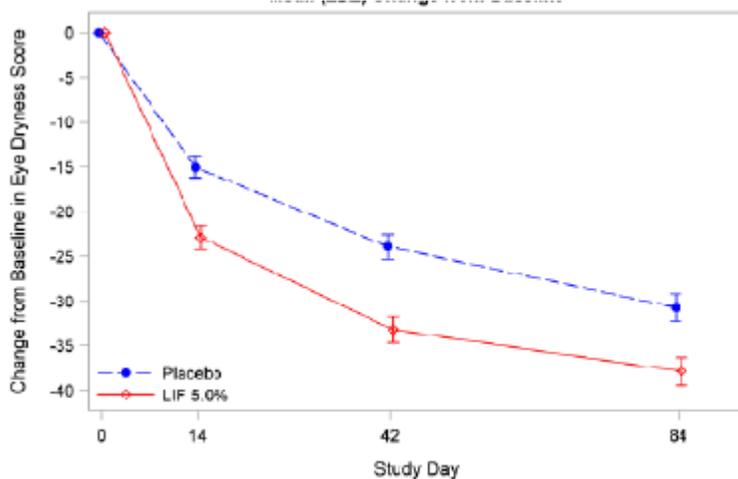
The primary endpoint was mean change from baseline to Day 84 in eye dryness score (VAS).

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

	<b>Vehicle N=356</b>	<b>5% LIF N=355</b>
<b>Baseline (Day 0)/ Visit 2</b>		
n	356	355
mean (SD)	69.0 (17.08)	68.3 (16.88)
<b>Day 84 (Week 12, Visit 5)</b>		
n	353	353
mean (SD)	38.35 (29.962)	30.43 (27.556)
<b>Change from Baseline to Day 84</b>		
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 ( $\pm$  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

**Reviewer’s Comment:**

*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.*

6.1.5 Analysis of Secondary Endpoints(s)

**KEY SECONDARY EFFICACY RESULTS**

**Table 6.1.5-1**  
**Eye Dryness Score at Day 42 (Visual Analogue Scale)**  
**ITT Population with LOCF**

	Vehicle N=356	5% LIF N=355
<b>Baseline (Day 0)/ Visit 2</b>		
n	356	355
mean (SD)	69.0 (17.08)	68.3 (16.88)
<b>Day 42 (Week 12, Visit 4)</b>		

	<b>Vehicle N=356</b>	<b>5% LIF N=355</b>
n	353	353
mean (SD)	45.2 (28.68)	35.1 (26.77)
<b>Change from Baseline to Day 42</b>		
n	353	353
Mean (SD)	-23.9 (25.99)	-33.2 (27.42)
Treatment effect (SE) <sup>a</sup>		9.32 (1.976)
95% confidence interval		(5.44, 13.20)
p-value (t-test)		<0.0001
<b>Day 14 (Week 12, Visit 3)</b>		
n	353	353
mean (SD)	54.1 (27.24)	45.5 (26.56)
<b>Change from Baseline to Day 14</b>		
n	353	353
Mean (SD)	-15.0 (22.40)	-22.9 (25.44)
Treatment effect (SE) <sup>a</sup>		7.85 (1.792)
95% confidence interval		(4.33, 11.37)
p-value (t-test)		<0.0001

a ANOVA model of change score with treatment, stratum and treatment by stratum interaction; weights set to stratum size.

Note: Eye dryness was scored on a VAS from 0-100 (0=no discomfort; 100=maximal discomfort).

Source: OPUS-3 CSR, Table 10. Section 14, Table 3.2.1.1 and Table 3.2.2.1.

**Reviewer’s Comment:**

*In the OPUS-3 study, the lifitegrast treatment group achieved statistically significant change from baseline in the eye dryness score (VAS) compared to the vehicle treatment group as early as Day 14, and also at Day 42.*

**OTHER SECONDARY ENDPOINTS**

- No statistically significant differences were observed between vehicle and lifitegrast in mean change from baseline to Day 14, Day 42 or Day 84, separately, in the ocular discomfort score of the study eye.
- A greater improvement was observed in the lifitegrast group at Day 42 in subject-reported itching (nominal significance p-value = 0.0318), in subject-reported foreign body sensation (nominal significance p-value = 0.0418), and in subject-reported eye discomfort (nominal significance p-value = 0.0048).
- The mean changes from baseline to Day 42 were similar between treatment groups for subject-reported burning/stinging, subject-reported photophobia, and subject-reported pain.

- The mean changes from baseline to Day 14 and to Day 84, separately, were similar between treatment groups for all VAS symptoms except for subject-reported eye dryness.

### 6.1.6 Other Endpoints

#### 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**

	<b>Vehicle N=356</b>	<b>5% LIF N=355</b>
<b>Baseline (Day 0)/ Visit 2</b>		
n	356	355
mean (SD)	2.46 (0.744)	2.46 (0.681)
<b>Day 84 (Week 12, Visit 5)</b>		
n	351	351
mean (SD)	1.81 (1.009)	1.66 (1.044)
<b>Change from Baseline to Day 84</b>		
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 <sup>a</sup>		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  $p=0.1402$ ).

**Reviewer's Comment:**

*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.*

**6.1.7 Subpopulations**

No meaningful differences were seen for the subgroups, and the results were consistent with the primary analysis.

**6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

Not applicable.

**6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with lifitegrast ophthalmic solution.

### 6.1.10 Additional Efficacy Issues/Analyses

#### **Comparison of Efficacy Results Across All Studies**

Refer also to Section 6.1.6 for the ad hoc analysis of sign data in OPUS-3.

**Table 6.1.10-1  
Summary of Key Elements of the Lifitegrast Clinical Efficacy Studies in Dry Eye Disease**

	<b>Phase 2</b>	<b>OPUS-1</b>	<b>OPUS-2</b>	<b>OPUS-3</b>
<b>Sample size</b>	230	588	718	711
<b>Primary sign</b>	ICSS	ICSS	ICSS	Not specified <sup>b</sup>
<b>Primary symptom</b>	None pre-specified	VR-OSDI score	EDS	EDS
<b>Study arms</b>	VEH and 0.1%, 1.0%, 5.0% LIF separately	VEH, 5.0% LIF	VEH, 5.0% LIF	VEH, 5.0% LIF
<b>Schedule</b>	BID for 84 days	BID for 84 days	BID for 84 days	BID for 84 days
<b>Key I/E</b>	<ul style="list-style-type: none"> <li>Adults with DED</li> <li>Cornea score of <math>\geq 2.0</math> in any eye</li> <li>Redness score <math>\geq 1.0</math> in <math>\geq 1</math> eye</li> <li>STT <math>\geq 1</math> and <math>\leq 10</math></li> <li>Change in ICSS <math>\geq +1</math> pre-post CAE</li> <li>ODS <math>\geq +3</math> at 2 consecutive time points intra-CAE</li> </ul>	<ul style="list-style-type: none"> <li>Adults with DED</li> <li>Cornea score of <math>\geq 2.0</math> in any eye</li> <li>Redness score <math>\geq 1.0</math> in <math>\geq 1</math> eye</li> <li>STT <math>\geq 1</math> and <math>\leq 10</math></li> <li>Change in ICSS <math>\geq +1</math> pre-post CAE</li> <li>ODS <math>\geq +3</math> at 2 consecutive time points intra-CAE</li> </ul>	<ul style="list-style-type: none"> <li>Adults with DED</li> <li>Cornea score of <math>\geq 2.0</math> in any eye</li> <li>Redness score <math>\geq 1.0</math> in <math>\geq 1</math> eye</li> <li>STT <math>\geq 1</math> and <math>\leq 10</math></li> <li>EDS <math>\geq 40</math> at screening and baseline</li> <li>ICSS <math>\geq 0.5</math> at screening and baseline</li> <li>Recent AT use required</li> </ul>	<ul style="list-style-type: none"> <li>Adults with DED</li> <li>Cornea score of <math>\geq 2.0</math> in any eye</li> <li>Redness score <math>\geq 1.0</math> in <math>\geq 1</math> eye</li> <li>STT <math>\geq 1</math> and <math>\leq 10</math></li> <li>EDS <math>\geq 40</math> at screening and baseline</li> <li>ICSS <math>\geq 0.5</math> at screening and baseline</li> <li>Recent AT use required</li> </ul>
<b>CAE</b>	Yes	Yes	No	No
<b>Rescue treatment allowed</b>	No	No	No	No
<b>Key sign measurements</b>	<ul style="list-style-type: none"> <li>Corneal fluorescein score</li> <li>Conjunctival lissamine green staining score</li> <li>STT</li> </ul>	<ul style="list-style-type: none"> <li>Corneal fluorescein score</li> <li>Conjunctival lissamine green staining score</li> <li>STT</li> </ul>	<ul style="list-style-type: none"> <li>Corneal fluorescein score</li> <li>Conjunctival lissamine green staining score</li> <li>STT</li> </ul>	<ul style="list-style-type: none"> <li>Not specified</li> </ul>

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	Phase 2	OPUS-1	OPUS-2	OPUS-3
<b>Key symptom measurements</b>	<ul style="list-style-type: none"> <li>• ODS</li> <li>• 7-item VAS <sup>a</sup></li> <li>• OSDI</li> </ul>	<ul style="list-style-type: none"> <li>• ODS</li> <li>• 7-item VAS <sup>a</sup></li> <li>• OSDI</li> </ul>	<ul style="list-style-type: none"> <li>• ODS</li> <li>• 7-item VAS <sup>a</sup></li> <li>• OSDI</li> </ul>	<ul style="list-style-type: none"> <li>• ODS</li> <li>• 7-item VAS <sup>a</sup></li> </ul>

a VAS symptoms: EDS, eye discomfort (OPUS-2 and OPUS-3 only), burning/stinging, itching, blurred vision (Phase 2 and OPUS-1 only), foreign body sensation, photophobia, and pain.

b An ad hoc analysis of the ICSS sign endpoint was performed to assess the consistency of this study with previous studies.

**Table 6.1.10-2**  
**Mean Baseline ICSS and EDS in the Phase 2, OPUS-1, OPUS-2, and OPUS-3 Studies (ITT Population)**

		Phase 2		OPUS-1		OPUS-2		OPUS-3	
Variable		VEH	LIF 5.0%	VEH	LIF 5.0%	VEH	LIF 5.0%	VEH	LIF 5.0%
<b>ICSS</b>	<b>n</b>	58	58	294	293	360	358	356	355
	<b>Mean (SD)</b>	1.65 (0.513)	1.77 (0.515)	1.81 (0.599)	1.84 (0.597)	2.40 (0.722)	2.39 (0.763)	2.46 (0.746)	2.46 (0.681)
	<b>Median (min, max)</b>	2.00 (0.5, 2.5)	2.00 (0.5, 3.0)	2.00 (0.5, 3.0)	2.00 (0.5, 3.0)	2.50 (0.5, 4.0)	2.50 (0.5, 4.0)	2.50 (0.5, 4.0)	2.50 (0.5, 4.0)
<b>EDS</b>	<b>n</b>	58	57	295	293	360	358	356	355
	<b>Mean (SD)</b>	51.81 (23.552)	51.58 (24.688)	41.62 (29.690)	40.18 (28.645)	69.22 (16.761)	69.68 (16.954)	68.96 (17.079)	68.31 (16.883)
	<b>Median (min, max)</b>	55.00 (0, 98.0)	51.00 (3.0, 100.0)	39.00 (0, 100.0)	42.00 (0, 100.0)	69.00 (40.0, 100.0)	69.00 (40.0, 100.0)	69.00 (40.0, 100.0)	67.00 (40.0, 100.0)

a VAS symptoms: EDS, eye discomfort (OPUS-2 and OPUS-3 only), burning/stinging, itching, blurred vision (Phase 2 and OPUS-1 only), foreign body sensation, photophobia, and pain.

**Reviewer’s Comment:**

*The mean baseline ICSS was highest in the OPUS-3 study followed by OPUS-2 and were considered to have moderate to severe (>2.0-4.0) disease. Subjects in the Phase 2 study and OPUS-1 had lower scores and were considered to have mild-to-moderate (0-2.0 points) disease.*

*These studies enrolled only subjects with a history of artificial tear use and EDS of >40 at baseline. The mean baseline EDS symptom score was highest at baseline in the OPUS-2 subject population followed closely by that in the OPUS-3 subjects.*

**Efficacy for the Treatment of Dry Eye Disease**

**Table 6.1.10-3**  
**ICSS in the Study Eye – Mean Change from Baseline to Day 84**  
**Phase 2, OPUS-1, OPUS-2 and OPUS-3 Studies**  
**ITT Population with LOCF**

	Phase 2			OPUS-1	OPUS-2	OPUS-3 <sup>c</sup>
	VEH (n=55) vs. LIF 0.1% (n=57)	VEH (n=55) vs. LIF 1.0% (n=55)	VEH (n=55) vs. LIF 5.0% (n=54)	VEH (n=294) <sup>a</sup> vs. LIF 5.0% (n=293)	VEH (n=360) vs. LIF 5.0% (n=358)	VEH (n=356) vs. LIF 5.0% (n=355)
<b>Treatment effect (95% CI)</b>	0.15 (-0.15, 0.46)	0.30 (0.01, 0.59)	0.35 (0.05, 0.65)	0.24 (0.10, 0.38)	0.03 (-0.10, 0.17)	0.17 <sup>c</sup> (0.03, 0.30)
<b>p-value</b>	0.3224 <sup>b</sup>	0.0433 <sup>b</sup>	0.0209 <sup>b</sup>	0.0007	0.6186	0.0144 <sup>c</sup>

ANOVA=analysis of variance; CI=confidence interval; ICSS=inferior corneal staining score; ITT=intent-to-treat; LIF=lifitegrast; LOCF=last observation carried forward; VEH=vehicle

Note: Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=few/rare punctate lesions; 2=discrete and countable lesions; 3=lesions too numerous to count, but not coalescent; 4=coalescent. Total score is derived sum of all regions (0-12 points).

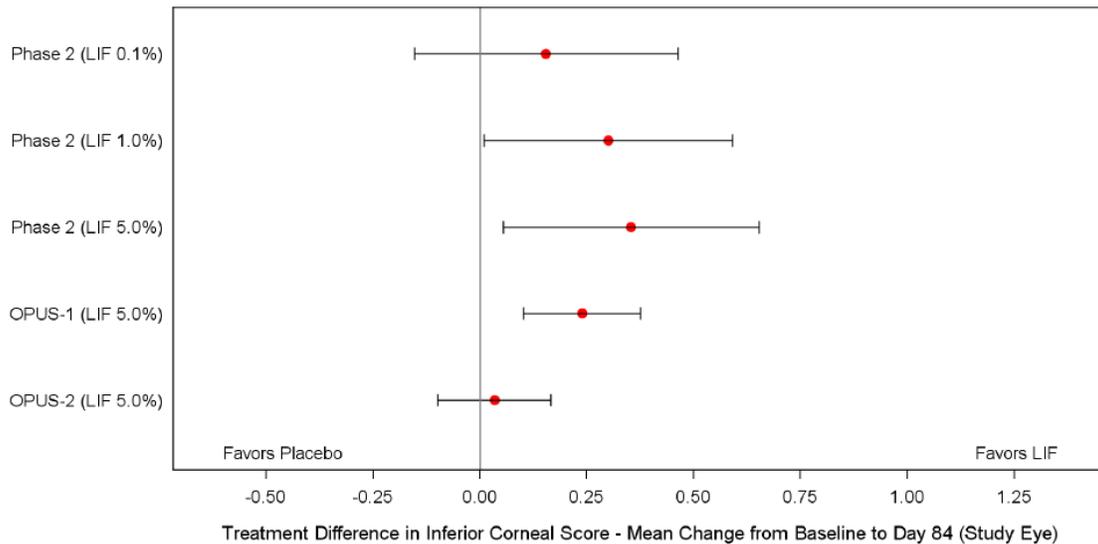
<sup>a</sup> ITT population for vehicle group is 295 subjects but 1 subject did not have a study eye designated due to a missed visit, therefore n=294 for vehicle group in analyses with evaluations of the study eye.

<sup>b</sup> Nominal p-value. Primary endpoint of Phase 2 was ICSS at Day 84. p-values from Phase 2 and OPUS-1 are from t-tests. p-value from OPUS-2 is from the ANOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.

<sup>c</sup> Nominal p-value. Inferior corneal staining score was not a prespecified endpoint in OPUS-3. An ad hoc analysis was performed per the Division's request to confirm previous results.

Source: Module 5.3.5.3, Table 3.1.1 and Table 3.1.9

**Figure 6.1.10-1**  
**Forest Plots of ICSS in the Study Eye – Treatment Differences (and 95% CIs)**  
**– Mean Change from Baseline to Day 84 in All Subjects in the Phase 2, OPUS-1, and**  
**OPUS-2 Studies (ITT Population with LOCF)**



Note: Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=few/rare punctate lesions; 2=discrete and countable lesions; 3=lesions too numerous to count, but not coalescent; 4=coalescent. Total score is derived sum of all regions (0-12 points).

Source: CSR Module 5.3.5.3, Figure 1.1.2

**Reviewer’s Comment:**

*The Phase 2 study demonstrated a dose response in mean change from baseline in ICSS at Day 84 (favoring 5% lifitegrast) with nominal statistical significance achieved for the 1.0% and 5.0% lifitegrast groups. Conducted under the same conditions, OPUS-1 demonstrated a statistically significant improvement in mean change from baseline to Day 84 in ICSS.*

*In a post hoc analysis of the phase 2 study, the subpopulation of subjects with previous artificial tear use was identified as having increased efficacy. Subsequent studies pre-specified this subpopulation (OPUS-1) and required this history (OPUS-2 and OPUS-3).*

*Thus, under different conditions (without the controlled adverse environment (CAE) and requiring previous artificial tear use and baseline EDS > 40 (see Table 6.1.10-1)), OPUS-2 showed a reduction in corneal staining favoring lifitegrast but not a statistically significant difference when compared to the vehicle group.*

*In the submission of OPUS-3 study which was similar in design to the OPUS-2 study, the difference in the change from baseline to Day 84 in the eye dryness score of the lifitegrast group compared to the vehicle group was statistically significant. 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 at the End of Review meeting) and demonstrated results in favor of lifitegrast and a nominal p-value of 0.0144.*

*In summary, replication of the sign and symptom endpoints was achieved in the four submitted studies of lifitegrast for the treatment of dry eye disease.*

- *A statistically significant treatment response for in the objective sign endpoint, change from baseline to Day 84 in inferior corneal staining score, was demonstrated for lifitegrast compared to vehicle in the Phase 2 and OPUS-1 studies. Additional replication was seen in the subgroup of subjects with a history of artificial tear use in both studies and 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 for lifitegrast compared to the vehicle 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 EDS symptoms in subjects treated with lifitegrast compared to vehicle was observed as early as Day 14 in OPUS-2 and OPUS-3.*

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

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.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

**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
<b>Phase 1</b>				
<b>Study SAR 1118-001</b>  PK and Safety	Randomized, double-masked, vehicle-controlled dose-escalation study	Lifitegrast 0.1, 0.3, 1, 5% or vehicle ophthalmic solution  <b>28 healthy subjects</b> (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

<b>Study Identifier</b>	<b>Study Description</b>	<b>Treatment Group</b>	<b>Dosing Regimen/ Duration</b>	<b>Endpoints</b>
<b>Phase 2</b>				
<b>Study 1118-ACJ-100</b>  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  <b>60 subjects with allergic conjunctivitis</b> (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
<b>Study 1118-KCS-100</b>  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)  <b>230 subjects with dry eye disease</b> (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)
<b>Phase 3</b>				
<b>Study 1118-KCS-200</b> SPD606-301; OPUS-1)  Safety and Efficacy	Multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution  <b>588 subjects</b> (142 males/ 446 females)	Single eye 1 drop BID for 84 days (12 weeks)	Copriary endpoints of ICSS (sign) and VR-OSDI score (symptom), each analyzed by mean change from baseline to Day 84 (Week 12)
<b>Study 1118-DRY-300</b> SPD606-302; OPUS-2)  Safety and Efficacy	Multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution  <b>718 subjects</b> (168 males/ 550 females)	Single eye 1 drop BID for 84 days (12 weeks)	Copriary endpoints of ICSS (sign) and EDS score (symptom), each analyzed by mean change from baseline to Day 84 (Week 12)

Study Identifier	Study Description	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Study 1118-DRY-400</b>  SPD606-303; SONATA)  Safety	Phase 3, multi-center, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution  <b>332 subjects with dry eye disease</b> (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
<b>Study SHP606-304</b>  OPUS-3)  Efficacy	Phase 3, multi-center, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 5% or vehicle ophthalmic solution  <b>711 subjects with dry eye disease</b> (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.

### 7.1.2 Categorization of Adverse Events

The routine clinical testing required to establish the safety of topical ophthalmic drops were adequately addressed in the design and conduct of this clinical trial.

All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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).

## 7.2 Adequacy of Safety Assessments

*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.*

*The safety data from OPUS-3 are consistent with that seen in the previous studies. No new safety signals were seen in this study.*

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

*No new safety signals were seen in this study.*

### 7.2.2 Explorations for Dose Response

Lifitegrast ophthalmic solution was administered in multiple dosage regimens. The highest dose tested during the clinical development was lifitegrast 5% three times daily. Adequate dose response information was obtained for the indication.

### 7.2.3 Special Animal and/or In Vitro Testing

None.

### 7.2.4 Routine Clinical Testing

*The routine clinical testing required to evaluate the safety concerns of lifitegrast ophthalmic solution 5% was adequately addressed in the design and conduct of these clinical trials. No new safety signals were seen in this study.*

### 7.2.5 Metabolic, Clearance, and Interaction Workup

*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).*

*Systemic absorption was low. No interaction studies were conducted. The safety data from OPUS-3 are consistent with that seen in the previous studies.*

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

None.

## 7.3 Major Safety Results

### 7.3.1 Deaths

*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.*

### 7.3.2 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 (%)
<b>Subjects with <math>\geq 1</math> serious TEAE</b>	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.

### 7.3.3 Dropouts and/or Discontinuations Not Previously Described

In OPUS-3, a total of 23 subjects were discontinued from treatment with the investigational product due to an ocular adverse event (vehicle: 6 subjects (1.7%); lifitegrast: 17 subjects (4.8%)). The most common ocular adverse reactions which led to treatment discontinuation were instillation site reaction (vehicle: 2 (0.6%); lifitegrast 5 (1.4%)) and instillation site irritation (vehicle: 0; lifitegrast 4 (1.1%)).

A total of 9 subjects were discontinued from treatment due to a non-ocular adverse event (vehicle: 3 (0.8%); lifitegrast: 6 (1.7%)). Each non-ocular adverse event that led to treatment discontinuation occurred in only 1 subject, with the exception of headache that occurred in 2 subjects in the lifitegrast group. No non-ocular adverse event which led to discontinuation occurred in  $\geq 1\%$  of subjects.

### 7.3.4 Significant Adverse Events

Refer to Section 7.4.1 for Common Adverse Events. No other significant adverse events were identified.

### 7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns were identified for the submission.

## 7.4 Supportive Safety Results

### 7.4.1 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 (%)
<b>Ocular TEAEs</b>		
Subjects with $\geq 1$ 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)
<b>Non-ocular TEAEs</b>		
Subjects with $\geq 1$ 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.

#### **Reviewer's Comment:**

*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 – 2**  
**Ocular Treatment Emergent Adverse Events in the Study Eye**  
**Occurring in ≥ 1% of Patients Receiving 5.0% Lifitegrast Dosed BID**  
**Safety Population**

MedDRA Preferred Term	Phase 2 Dry Eye (N=58)	OPUS-1 (n=293)	OPUS-2 (n=359)	OPUS-3 (n=357)	SONATA (n=220)	Phase 2 Dry Eye (N=58)	OPUS-1 (n=295)	OPUS-2 (n=359)	OPUS-3 (n=354)	SONATA (n=111)
	Lifitegrast 5% BID					Vehicle BID				
<b>At least One Ocular TEAE</b>	<b>40 (69.0%)</b>	<b>174 (59.4%)</b>	<b>121 (33.7%)</b>	<b>141 (39.5%)</b>	<b>118 (53.6%)</b>	<b>15 (25.9%)</b>	<b>75 (25.4%)</b>	<b>59 (16.4%)</b>	<b>63 (17.8%)</b>	<b>38 (34.2%)</b>
Instillation site irritation	20 (34.5%)	69 (23.5%)	28 (7.8%)	65 (18.2%)	33 (15.0%)	6 (10.3%)	12 (4.1%)	5 (1.4%)	11 (3.1%)	5 (4.5%)
Instillation site reaction	8 (13.8%)	50 (17.1%)	25 (7.0%)	45 (12.6%)	29 (13.2%)	0	2 (0.7%)	4 (1.1%)	19 (5.4%)	2 (1.8%)
Instillation site pain	20 (34.5%)	63 (21.5%)	11 (3.1%)	8 (2.2%)	7 (3.2%)	3 (5.2%)	11 (3.7%)	3 (0.8%)	0	2 (1.8%)
Visual acuity reduced	1 (1.7%)	14 (4.8%)	18 (5.0%)	2 (0.6%)	25 (11.4%)	3 (5.2%)	15 (5.1%)	23 (6.4%)	1 (0.3%)	7 (6.3%)
Instillation site pruritus	2 (3.4%)	19 (6.5%)	8 (2.2%)	8 (2.2%)	5 (2.3%)	0	6 (2.0%)	0	2 (0.6%)	1 (0.9%)
Lacrimation increased	2 (3.4%)	7 (2.4%)	9 (2.5%)	9 (2.5%)	8 (3.6%)	0	1 (0.3%)	1 (0.3%)	2 (0.6%)	2 (1.8%)
Eye irritation	0	4 (1.4%)	11 (3.1%)	10 (2.8%)	8 (3.6%)	0	3 (1.0%)	1 (0.3%)	5 (1.4%)	1 (0.9%)
Vision blurred	0	3 (1.0%)	10 (2.8%)	8 (2.2%)	9 (4.1%)	1 (1.7%)	3 (1.0%)	2 (0.6%)	2 (0.6%)	4 (3.6%)
Eye pain	1 (1.7%)	6 (2.0%)	5 (1.4%)	5 (1.4%)	7 (3.2%)	0	5 (1.7%)	1 (0.3%)	2 (0.6%)	0
Ocular hyperemia	2 (3.4%)	7 (2.4%)	4 (1.1%)	3 (0.8%)	4 (1.8%)	0	4 (1.4%)	2 (0.6%)	0	0
Conjunctival hemorrhage	3 (5.2%)	2 (0.7%)	4 (1.1%)	2 (0.6%)	1 (0.5%)	0	2 (0.7%)	1 (0.3%)	2 (0.6%)	1 (0.9%)
Instillation site foreign body sensation	2 (3.4%)	0	3 (0.8%)	4 (1.1%)	6 (2.7%)	0	2 (0.7%)	0	8 (2.3%)	0
Eye pruritus	0	5 (1.7%)	4 (1.1%)	5 (1.4%)	8 (3.6%)	1 (1.7%)	2 (0.7%)	4 (1.1%)	5 (1.4%)	2 (1.8%)
Instillation site lacrimation	1 (1.7%)	7 (2.4%)	1 (0.3%)	0	3 (1.4%)	0	1 (0.3%)	0	0	1 (0.9%)

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Lifitegrast Ophthalmic Solution, 5%

MedDRA Preferred Term	Phase 2 Dry Eye (N=58)	OPUS-1 (n=293)	OPUS-2 (n=359)	OPUS-3 (n=357)	SONATA (n=220)	Phase 2 Dry Eye (N=58)	OPUS-1 (n=295)	OPUS-2 (n=359)	OPUS-3 (n=354)	SONATA (n=111)
	Lifitegrast 5% BID					Vehicle BID				
Conjunctival hyperemia	0	1 (0.3%)	5 (1.4%)	4 (1.1%)	6 (2.7%)	1 (1.7%)	1 (0.3%)	4 (1.1%)	1 (0.3%)	4 (3.6%)
Photophobia	0	7 (2.4%)	4 (1.1%)	5 (1.4%)	1 (0.5%)	0	0	0	1 (0.3%)	0
Eye discharge	0	1 (0.3%)	3 (0.8%)	5 (1.4%)	4 (1.8%)	1 (1.7%)	1 (0.3%)	0	0	1 (0.9%)
Drug ineffective (Dry eye)	1 (1.7%)	0	2 (0.6%)	0	4 (1.8%)	1 (1.7%)	2 (0.7%)	2 (0.6%)	1 (0.3%)	6 (5.4%)
Instillation site discomfort	1 (1.7%)	0	0	0	3 (1.4%)	0	0	0	0	0
Eyelid margin crusting	0	2 (0.7%)	5 (1.4%)	3 (0.8%)	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.9%)
Foreign body sensation	0	4 (1.4%)	1 (0.3%)	4 (1.1%)	0	0	2 (0.7%)	1 (0.3%)	2 (0.6%)	0
Blepharitis	0	2 (0.7%)	4 (1.1%)	0	2 (0.9%)	0	2 (0.7%)	0	0	0
Vitreous detachment	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (1.4%)	0	0	0	0	0
Glaucoma	1 (1.7%)	0	0	0	1 (0.5%)	0	0	0	0	0
Erythema of eyelid	1 (1.7%)	0	0	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.9%)
Eye infection	1 (1.7%)	0	0	0	0	0	0	0	0	0
Eyelid irritation	1 (1.7%)	0	0	0	0	0	0	0	0	0
Seasonal allergy	0	0	0	0	3 (1.4%)	0	0	0	0	0

Sources: CSR 1118-KCS-100, Module 5.3.5.1, Tables 14.3.1.2 and 14.3.1.3; CSR 1118-DRY-300, Module 5.3.5.1, Tables 4.2.2 and 4.2.3; CSR SHP606-304, Module 5.3.5.1, Tables 4.2.2 and 4.2.3; CSR 1118-KCS-200, Module 5.3.5.1, Tables 4.2.2 and 4.2.3; CSR 1118-DRY-400 Module 5.3.5.1 Tables 4.2.2 and 4.2.3.

**Table 7.4.1 – 3**  
**Non-Ocular Treatment Emergent Adverse Events in the Study Eye**  
**Occurring in ≥ 1% of Patients Receiving 5.0% Lifitegrast in Any Study**  
**Safety Population**

MedDRA Preferred Term	Phase 2 Dry Eye (N=58)	OPUS-1 (n=293)	OPUS-2 (n=359)	OPUS-3 (n=357)	SONATA (n=220)	Phase 2 Dry Eye (N=58)	OPUS-1 (n=295)	OPUS-2 (n=359)	OPUS-3 (n=354)	SONATA (n=111)
	Lifitegrast 5% BID					Vehicle BID				
<b>At least One Non-Ocular TEAE</b>	<b>19 (32.8%)</b>	<b>106 (36.2%)</b>	<b>96 (26.7%)</b>	<b>84 (23.5%)</b>	<b>104 (47.3%)</b>	<b>22 (37.9%)</b>	<b>77 (26.1%)</b>	<b>45 (12.5%)</b>	<b>29 (8.2%)</b>	<b>40 (36.0%)</b>
Dysgeusia	7 (12.1%)	39 (13.3%)	58 (16.2%)	46 (12.9%)	36 (16.4%)	0	0	1 (0.3%)	1 (0.3%)	2 (1.8%)
Nasopharyngitis	2 (3.4%)	19 (6.5%)	3 (0.8%)	1 (0.3%)	6 (2.7%)	2 (3.4%)	26 (8.8%)	2 (0.6%)	0	2 (1.8%)
Headache	1 (1.7%)	7 (2.4%)	7 (1.9%)	5 (1.4%)	9 (4.1%)	1 (1.7%)	0	5 (1.4%)	2 (0.6%)	0
Influenza	3 (5.2%)	0	1 (0.3%)	1 (0.3%)	2 (0.9%)	0	0	1 (0.3%)	0	0
Depression	2 (3.4%)	2 (0.7%)	0	0	4 (1.8%)	0	1 (0.3%)	0	0	1 (0.9%)
Sinusitis	0	2 (0.7%)	1 (0.3%)	4 (1.1%)	7 (3.2%)	2 (3.4%)	4 (1.4%)	1 (0.3%)	3 (0.8%)	2 (1.8%)
Urinary tract infection	1 (1.7%)	0	3 (0.8%)	1 (0.3%)	4 (1.8%)	0	4 (1.4%)	1 (0.3%)	3 (0.8%)	3 (2.7%)
Hypertension	1 (1.7%)	3 (1.0%)	2 (0.6%)	0	1 (0.5%)	0	2 (0.7%)	0	0	0
Influenza-like illness	1 (1.7%)	2 (0.7%)	1 (0.3%)	0	1 (0.5%)	1 (1.7%)	2 (0.7%)	1 (0.3%)	0	0
Bronchitis	0	5 (1.7%)	0	0	2 (0.9%)	3 (5.2%)	1 (0.3%)	0	0	1 (0.9%)
Arthralgia	0	1 (0.3%)	0	0	5 (2.3%)	0	1 (0.3%)	0	1 (0.3%)	0
Hypothyroidism	1 (1.7%)	0	1 (0.3%)	0	1 (0.5%)	0	0	1 (0.3%)	1 (0.3%)	0
Upper respiratory tract infection	0	0	2 (0.6%)	1 (0.3%)	3 (1.4%)	0	1 (0.3%)	4 (1.1%)	0	2 (1.8%)
Foot fracture	1 (1.7%)	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0	0
Cough	1 (1.7%)	0	0	1 (0.3%)	0	1 (1.7%)	0	0	0	3 (2.7%)
Herpes zoster	1 (1.7%)	1 (0.3%)	0	0	0	0	1 (0.3%)	1 (0.3%)	2 (0.6%)	0

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MedDRA Preferred Term	Phase 2 Dry Eye (N=58)	OPUS-1 (n=293)	OPUS-2 (n=359)	OPUS-3 (n=357)	SONATA (n=220)	Phase 2 Dry Eye (N=58)	OPUS-1 (n=295)	OPUS-2 (n=359)	OPUS-3 (n=354)	SONATA (n=111)
	Lifitegrast 5% BID					Vehicle BID				
Sinus congestion	0	1 (0.3%)	0	1 (0.3%)	3 (1.4%)	0	0	0	0	0
Dyspnea	0	0	1 (0.3%)	0	3 (1.4%)	0	0	0	0	0
Gastroesophageal reflux disease	0	0	1 (0.3%)	0	3 (1.4%)	0	0	0	0	0
Folliculitis	1 (1.7%)	0	0	0	0	0	0	0	0	0
Osteoarthritis	0	1 (0.3%)	0	0	3 (1.4%)	1 (1.7%)	0	2 (0.6%)	1 (0.3%)	2 (1.8%)
Tachycardia	1 (1.7%)	0	0	0	0	0	0	1 (0.3%)	0	1 (0.9%)
Urinary retention	1 (1.7%)	0	0	0	0	0	0	0	0	0
Asthma	0	0	0	0	3 (1.4%)	2 (3.4%)	0	1 (0.3%)	0	0
Drug dispensing error	0	0	0	5 (1.4%)	0	0	0	0	2 (0.6%)	
Intervertebral disc protrusion	0	0	0	0	3 (1.4%)	0	1 (0.3%)	0	0	1 (0.9%)
Restless legs syndrome	0	0	0	0	3 (1.4%)	0	0	0	0	0
Seasonal allergy	0	0	0	0	3 (1.4%)	0	1 (0.3%)	0	0	2 (1.8%)

Sources: CSR 1118-KCS-100, Module 5.3.5.1, Tables 14.3.1.2 and 14.3.1.3; CSR 1118-DRY-300, Module 5.3.5.1, Tables 4.2.2 and 4.2.3; CSR SHP606-304, Module 5.3.5.1, Tables 4.2.2 and 4.2.3; CSR 1118-KCS-200, Module 5.3.5.1, Tables 4.2.2 and 4.2.3; CSR 1118-DRY-400 Module 5.3.5.1 Tables 4.2.2 and 4.2.3.

**Table 7.4.1-4  
Treatment Emergent Adverse Events  
Occurring in  $\geq 1\%$  in Vehicle or Lifitegrast 5% Treatment Groups  
All Dry Eye Studies – Safety Population**

Preferred Term	Vehicle N=1177 n (%)	5% LIF N=1287 n (%)
<b>Ocular Treatment Emergent Adverse Reactions</b>		
<b>Subjects with at least 1 Ocular TEAE</b>	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)
<b>Non-ocular Treatment Emergent Adverse Reactions</b>		
<b>Subjects with at least 1 Non-Ocular TEAE</b>	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.

**Reviewer's Comment:**

*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  $\geq 5\%$  of subjects were: dysgeusia (15%), instillation site irritation (15%), instillation site reaction (12%), instillation site pain (10%) and visual acuity reduced (5%).*

*The treatment emergent adverse reactions which occurred in between 1% and 5% of subjects and more frequently in the lifitegrast group compared to the vehicle group were, in descending order: eye irritation (3%), instillation site pruritus (3%), lacrimation increased (3%), vision blurred (3%), eye pain (2%), eye pruritus (2%), headache (2%), ocular hyperemia (2%), conjunctival hyperemia (1%), eye discharge (1%), instillation site foreign body sensation (1%), and sinusitis (1%).*

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

#### 7.4.2 Laboratory Findings

*Clinical laboratory evaluations were only conducted in the Phase 1 study and as part of a substudy in the SONATA study.*

*No safety signals were seen in this study.*

#### 7.4.3 Vital Signs

*Vital signs were not obtained during this study.*

*No safety signals were seen in this study.*

#### 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed during any of these studies.

#### 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this product.

#### 7.4.6 Immunogenicity

Immunogenicity testing was not performed during the clinical development of lifitegrast.

### 7.5 Other Safety Explorations

*No new safety signals were seen in this study.*

### 7.5.1 Dose Dependency for Adverse Events

Lifitegrast ophthalmic solution was evaluated at multiple dose levels during clinical development. Instillation site discomfort was dose dependent.

### 7.5.2 Time Dependency for Adverse Events

Lifitegrast does not have a delayed onset of action. Exploration of time to onset was not conducted.

### 7.5.3 Drug-Demographic Interactions

Analyses by age, sex and race were performed on the 12-Week Dry Eye Studies Pool. The overall safety profile was consistent across age, sex, and race subgroups. The studies did not include any subjects younger than 19 years of age.

### 7.5.4 Drug-Disease Interactions

A review of adverse events by subpopulations categorized by concomitant diseases revealed no safety concerns.

### 7.5.5 Drug-Drug Interactions

No drug interaction studies have been conducted during the lifitegrast clinical development program.

## 7.6 Additional Safety Evaluations

*No new safety signals were seen in this study.*

### 7.6.1 Human Carcinogenicity

There have been no lifitegrast studies performed which suggest a tumorigenic potential.

### 7.6.2 Human Reproduction and Pregnancy Data

No subjects had positive pregnancy tests during the OPUS-3 study.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

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 PeRC on May 14, 2015. PeRC concurred clinical studies in this population are impractical (see above).

## 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with lifitegrast. No reports of overdose were received during the clinical studies.

## 7.7 Additional Submissions / Safety Issues

*The 4-Month Safety Update has not yet been submitted.*

## 8 Postmarket Experience

Lifitegrast is not a marketed drug product. There are no postmarketing data to report.

## 9 Appendices

### 9.1 Literature Review/References

An independent literature review did not produce any additional significant information regarding lifitegrast.

### 9.2 Advisory Committee Meeting

The application did not raise any issues which were thought to benefit from a discussion at an Advisory Committee meeting.

### 9.3 Clinical Investigator Financial Disclosure

#### Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 208-073

Submission Date(s): January 22, 2016

Applicant: Shire Development, LLC.

Product: Xiidra (lifitegrast ophthalmic solution) 5.0%

Reviewer: Rhea A. Lloyd, MD

Date of Review: February 4, 2016

Covered Clinical Studies (Name and/or Number):  
SHP606-304 (OPUS-3)

Clinical Review  
 Rhea A. Lloyd, MD  
 NDA 208-073  
 Lifitegrast Ophthalmic Solution, 5%

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: Study SHP-304: 42 investigators with 191 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>Two.</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>None</u> Significant payments of other sorts: <u>Two</u> Proprietary interest in the product tested held by investigator: <u>None</u> Significant equity interest held by investigator in sponsor of covered study: <u>None</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from applicant)

**Disclosure: Financial Interests and Arrangements of Clinical Investigators**

STUDY SHP606-304 (OPUS-3)			
A Phase 3, Multicenter, Randomized, Double-masked, and Placebo-controlled Study			
Site Number/Name	Name	Study Responsibility	Financial Interest Disclosed?
(b) (6)	(b) (6)	Principle Investigator	Yes, approximately \$43,000 USD associated with Advisory Board/consulting
Number of Subjects Enrolled = (b) (6)	(b) (6)		
(b) (6)	(b) (6)	Principle Investigator	Yes, Approximately \$74,000 USD associated with Advisory Board/consulting
(b) (6)	(b) (6)		
Number of Subjects Enrolled = (b) (6)	(b) (6)		

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

*Shire believes that the Covered Clinical Trials (as define in 21 CFR 54.2) contained in this New Drug Application (NDA) for lifitegrast under NDA 208,073 are free of potential bias, regardless of the disclosed financial interests of our clinical investigators.*

*The design of SHP606-304 (OPUS-3) minimized the potential for bias by any investigator. By the study design, there was no single investigator or sub-investigator who had influence that could affect the results of the trial. The key factors included in the study design for SHP606-304 which contributed to the minimization of potential bias are described below:*

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<sup>1</sup> See [web address].

- *Study SHP606-304 included in this submission is a double-blind randomized trial. The actual treatment given to individual subjects is determined by a randomization schedule. In no instance should an investigator treating patients in these trials have known the sequence of potential treatment assignments. Per protocol the randomization code in these trials was not to be broken except in emergency situations.*
- *The study protocol was reviewed and approved by the Institutional Review Board (IRBs) before its initiation in order to ensure that financial interests of the trial investigators did not compromise the protection of research subjects.*
- *The clinical trial was monitored by an external Contract Research Organization according to the principles of Good Clinical Practice.*

### **9.3 Labeling Recommendations**

Following is the applicant's proposed labeling submitted in the January 22, 2016, submission.

The reviewer's additions are noted in underline and deletions by.

19 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.**  
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/s/  
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RHEA A LLOYD  
04/26/2016

WILLIAM M BOYD  
04/27/2016

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

<b>NDA/BLA Number:</b> 208073	<b>Applicant:</b> Shire Development, LLC	<b>Stamp Date:</b> January 22, 2016
<b>Drug Name:</b> Xiidra (lifitegrast ophthalmic solution) 5.0%	<b>NDA/BLA Type:</b> Class 2 Resubmission	

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?  Study Number: 1118-KCS-100 Study Title: A Phase 2, Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Efficacy of Three Different Concentrations (0.1%, 1.0%, 5.0%) of SAR 1118 Ophthalmic Solution in Subjects with Dry Eye Using the Controlled Adverse Environment (CAE) Model  Sample Size: 230 subjects                      Arms: 3 Submitted in Original NDA (February 25, 2015): Module 5.3.5.1				
<b>EFFICACY</b>					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Yes. This is a Class 2 Resubmission.  Pivotal Study #1: SHP606-304 (OPUS-3) Indication: Treatment of dry eye	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Topical ophthalmic drug. More than 300 subjects exposed at the proposed dose.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant requested a Full Waiver of pediatric assessment. This application was presented at the Pediatric Review Committee (PeRC) on May 14, 2015. PeRC concurred clinical studies in this population are impractical.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			See Statistical filing review for details.
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

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Reviewing Medical Officer Date

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Clinical Team Leader Date

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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.**  
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/s/  
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RHEA A LLOYD  
03/01/2016

WILLIAM M BOYD  
03/01/2016

Deputy Office Director Decisional Memo

<b>Date</b>	(electronic stamp)
<b>From</b>	John Farley, M.D.,M.P.H.
<b>Subject</b>	Deputy Office Director Decisional Memo
<b>NDA #</b>	208073
<b>Applicant Name</b>	Shire Development, LLC
<b>Date of Submission</b>	February 25, 2015
<b>PDUFA Goal Date</b>	October 25, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Xiidra / lifitegrast ophthalmic solution 5%
<b>Dosage Forms / Strength</b>	Topical ophthalmic solution
<b>Proposed Indication</b>	Treatment of the signs and symptoms of dry eye disease
<b>Action:</b>	Complete Response

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Medical Officer Review	Rhea A. Lloyd, M.D.
Statistical Review	Solomon Chefo, Ph.D.
Pharmacology Toxicology Review	Maria Rivera, Ph.D.
Product Quality Review Technical Lead	Anamitro Banerjee, Ph.D.
Clinical Pharmacology Review	Gerlie Gieser, Ph.D.
Division of Pediatric and Maternal Health Memorandum	Suchitra Balakrishnan, M.D., Ph.D.
CDTL Review	William M. Boyd, M.D.
Deputy Division Director Review	Wiley Chambers, M.D.

OND=Office of New Drugs  
CDTL=Cross-Discipline Team Leader

## 1. Introduction

Lifitegrast (LIF) ophthalmic solution 5% is an antagonist of LFA-1 (also known as CD11a/CD18 or  $\alpha$ L $\beta$ 2) formulated as an unpreserved (b) (4) sterile eye drop. LIF binds to LFA-1 targets T-cell surface antigen and prevents interaction with its cognate ligand, ICAM-1 (also known as CD54). Inhibition of LFA-1/ICAM-1 interaction results in the diminished recruitment of leukocytes to sites of inflammation and reduces the activation of leukocytes resulting in a reduction of the expression of proinflammatory cytokines. LIF is a new molecular entity.

The applicant submitted this NDA seeking the indication of “the treatment of the signs and symptoms of dry eye disease (b) (4)”.

The proposed dosing regimen is one drop twice a day in each eye.

The efficacy review for this NDA relies upon the results of three multicenter, randomized, double-masked, vehicle-controlled safety and efficacy studies conducted in adult subjects with dry eye disease: the Phase 2 Study 1118-KCS-100, the Phase 3 Study 1118-KCS-200 (OPUS-1), and the Phase 3 Study 1118-DRY-300 (OPUS-2). In addition, the Phase 3 Study 1118-DRY-400 (SONATA) was conducted to evaluate the safety of administration of one year duration.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of LIF ophthalmic solution 5% for the indication proposed. For a detailed discussion of NDA 208073, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Deputy Division Director Review.

## 2. Background/Regulatory

There are currently no ophthalmic drug products approved for the treatment of signs and symptoms of dry eye disease.

LIF ophthalmic solution was studied under IND 77885. A series of meetings were held between the applicant and the Agency regarding the development of this new drug. On May 15, 2014, a Pre-NDA meeting was held with the applicant. The results of the LIF clinical development program and proposed clinical data package for a NDA were discussed. Based on the results of the clinical trials discussed (the Phase 2 Study KCS-100, OPUS-1, and OPUS-2), the Division recommended that the applicant consider conducting another trial to provide evidence of efficacy.

## 3. Chemistry Manufacturing and Controls / Product Quality Microbiology

The Product Quality Review was provided by a team of reviewers with Dr. Banerjee serving as the technical lead for the NDA. The application was not recommended for approval by the product quality review team. The product quality deficiencies are

detailed in the Product Quality Review. For the drug substance, the acceptance criterion for (b) (4) was not acceptable. For the drug product, specifications for potential leachables were not acceptable. Manufacturing facilities were assessed as acceptable. There were no product quality microbiology deficiencies. I concur that product quality deficiencies preclude approval.

#### 4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology Reviewer identified approvability issues related to the product quality deficiencies. She recommended that the applicant reduce the specification for (b) (4), a potentially genotoxic impurity, to as low as reasonably possible. In addition, 3 leachables were found in a developmental stability batch and primary stability batches at levels above (b) (4) ppm. She recommended that the applicant identify these leachables and provide safety data to support these levels. I concur that pharmacology toxicology deficiencies preclude approval.

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 reviewer noted that, although exposure margins were low, the mild and transient nature of the findings did not present a major clinical concern and were consistent with adverse reactions noted in human clinical trials.

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. The reviewer noted that based on AUC, the exposure margin for these findings is 660-fold, indicating no clinical concern.

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 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 sternbrae at the mid dose and high dose. For both of these studies, the reviewer noted that based on AUC, the exposure margin was 400-fold at the 3mg/kg/day dose, indicating minimal clinical concern.

#### 5. Clinical Pharmacology

The Clinical Pharmacology Reviewer found the NDA acceptable, and I concur that there are no clinical pharmacology issues precluding approval.

The clinical pharmacology data in this NDA consists of plasma PK and tear fluid PK in healthy subjects enrolled in a Phase 1 study, sparse plasma PK and PD (lymphocyte counts) in a subset of dry eye disease patients enrolled in the SONATA study, and *in vitro* data on LIF metabolism in human hepatocytes, protein binding, and CYP2C9 inhibitory potential, as well as *in vitro* primary pharmacodynamic and cardiovascular safety pharmacology.

In the Phase 1 study, plasma LIF concentrations were below the LLOQ (0.5 ng/mL) of the PK assay after the 1 hour timepoint. In the SONATA study, there was no evidence of accumulation of LIF in plasma over time. In the SONATA trial, 47 patients treated with the proposed commercial LIF 5% ophthalmic solution (1 drop twice daily) were included in the PK and PD substudy; LIF trough concentrations were measured on Days 180 and 360, and lymphocyte (CD3, CD4, and CD8) counts were measured on Days 0 (pretreatment), 180 and 360. In the 9 patients with detectable ( $\geq 0.5$  ng/mL) plasma LIF trough concentrations ( $C_{\text{trough}}$ ), 2 had pre-dose concentrations that exceeded the EC50 (2.5 ng/mL) for inhibiting T-cell adhesion *in vitro*, and an additional patient had a CD8 count  $< 220/\mu\text{L}$  measured on Day 180. The applicant stated that these 3 patients did not experience systemic infections or immunosuppressive complications during the 12 month treatment period.

## 6. Clinical Microbiology

Not Applicable

## 7. Clinical/Statistical Efficacy

The Clinical Reviewer, Statistical Reviewer, CDTL, and Deputy Division Director all concluded that substantial evidence of efficacy has not been provided, and I concur.

The Phase 2 Study KCS-100, Study OPUS-1, and Study OPUS-2 were submitted to provide evidence of efficacy. The three studies were multicenter, randomized, double-masked, vehicle-controlled studies conducted in adult subjects with dry eye disease in the U.S. and were similar in design. Each study was 14 weeks in duration with five study visits at Days -14, 0, 14, 42, and 84. There was a two week open label vehicle run-in screening period followed by a 12 week treatment period. Treatment in each study was administered as a single drop twice daily (AM and PM) in each eye for 12 weeks. For each study, the primary analysis was performed in the ITT population using the last observation carried forward (LOCF) method for imputing missing data.

In the Phase 2 Study KCS-100, 230 subjects with dry eye were randomized to LIF 0.1, 1, 5% or vehicle ophthalmic solution. The primary efficacy endpoint was a sign of dry eye disease, inferior corneal staining score (ICSS), of the designated study eye at Day 84. The primary efficacy analysis was a pairwise comparison between the three concentrations of LIF ophthalmic solution (LIF 0.1%, 1%, and 5%) against vehicle. None of the LIF groups achieved a statistically significant difference in the inferior corneal staining score at Day 83 compared to vehicle. Based on change from baseline, the

applicant concluded that the greatest treatment effect was observed with the LIF 5% dose, and this was the dose chosen to be studied in OPUS-1 and OPUS-2.

In the OPUS-1 Study, 588 subjects were randomized to LIF 5% or vehicle. The primary efficacy co-primary endpoints were the sign endpoint of the mean change in ICCS from baseline at Day 84 and the patient-reported symptom endpoint of Ocular Surface Disease Index (OSDI) score mean change from baseline at Day 84. The mean change in ICSS at Day 84 in the LIF 5% treated group was -0.07 (95% CI: -0.17, -0.04) and in the vehicle treated group was +0.17 (95% CI: 0.07, 0.26); the treatment difference (LIF 5.0% minus vehicle) was -0.23 (95% CI: -0.36, -0.09) and a statistically significant difference was achieved for this component of the co-primary endpoint (p-value = 0.0007). Both groups showed small and comparable mean reductions in OSDI score from baseline throughout the study. The mean change in OSDI score at Day 84 in the LIF 5% treated group was -0.11 (95% CI: -0.20, -0.01) and in the vehicle group was -0.12 (95% CI: -0.21, -0.04); the treatment difference was -0.01 (95% CI: -0.12, 0.10) and not statistically significant (p-value = 0.8261). Thus, the OPUS-1 Study failed the co-primary endpoint.

The patient reported Eye Dryness Score (EDS) was a secondary endpoint for the OPUS-1 Study. In OPUS-1, the mean change in EDS at Day 84 in the LIF 5% treated group was -15.2 (95% CI: -18.8, -11.6) and in the vehicle treated group was -11.2 (95% CI: -14.5, -7.9); the treatment difference was -4.7 (95% CI: -8.9, -0.4; p-value = 0.0311). A numerically larger improvement in EDS from baseline at Day 84 was seen in a small subgroup of subjects with a recent history of artificial tear use and with baseline EDS  $\geq 40$ . This informed the design of the OPUS-2 Study.

In the OPUS-2 Study, 718 subjects were randomized to LIF 5% or vehicle. Based on history of artificial tear use and patient-reported symptom scores, the OPUS-2 Study enrolled subjects who were somewhat more symptomatic than the subjects enrolled in the Phase 2 Study or OPUS-1. The primary efficacy co-primary endpoints were the mean change in ICCS from baseline at Day 84 and the patient-reported symptom endpoint of the mean change in EDS from baseline at Day 84. Both LIF and vehicle groups showed numerically larger mean reductions in ICSS throughout the study compared with the Phase 2 and OPUS-1 studies. In OPUS-2, both groups demonstrated comparable mean reductions in ICSS at Day 84: the mean change in ICSS at Day 84 in the LIF 5% treated group was -0.73 (95% CI: -0.83, -0.64) and in the vehicle group was -0.71 (95% CI: -0.80, -0.61); the treatment difference was -0.03 (95% CI: -0.16, 0.10) and not statistically significant (p-value = 0.6122) for this component of the co-primary endpoint. The mean change in EDS at Day 84 in the LIF 5% treated group was -35.3 (95% CI: -38.3, -32.3) and in the vehicle group was -22.8 (95% CI: -25.7, -19.8); the treatment difference was -12.3 (95% CI: -16.4, -8.3) and was statistically significant (p-value < 0.0001) for this component of the co-primary endpoint. With the failure of the ICSS component of the co-primary endpoint, the OPUS-2 study failed the co-primary endpoint. In the OPUS-2 Study, the discontinuation rate in the LIF 5% treated group was higher than in the vehicle group (10% versus 3% in vehicle). Adverse event was the most common reason for discontinuation in the LIF 5% treated group (7% versus 1.0% for vehicle). A sensitivity analysis imputing all missing data as failure was performed and the results were consistent with the primary efficacy analysis.

In summary, the submitted studies failed their primary efficacy endpoints, and there is a lack of consistency between the ICSS and patient reported symptom measures. At least one additional adequate and well-controlled trial would be needed to provide substantial evidence of efficacy.

## **8. Safety**

The Clinical Reviewer, Statistical Reviewer, CDTL, and Deputy Division Director all concluded that there were no safety concerns precluding approval, and I concur with this conclusion.

In the 12 week comparative studies, a total of 710 patients were exposed to LIF and 712 patients were in the vehicle comparator groups. In the one year duration SONATA Study, 220 patients were exposed to LIF and 111 patients were in the vehicle comparator group. There were 2 deaths in the safety data base unrelated to study drug, and a Serious Adverse Event rate of approximately 1% in both LIF and vehicle groups. Serious Adverse Events reported were considered by the Clinical Reviewer to be not related to study drug and common in the age group studied, and I concur.

The treatment emergent adverse reactions which occurred in  $\geq 5\%$  of subjects and more frequently in the LIF 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%). The treatment emergent adverse reactions which occurred in between 1% and 5% of subjects and more frequently in the LIF group compared to the vehicle group were: instillation site pruritus (3%), lacrimation increased (3%), vision blurred (3%), eye irritation (2%), eye pain (2%), eye pruritus (2%), headache (2%), ocular hyperemia (2%), conjunctival hemorrhage (1%), instillation site foreign body sensation (1%), and instillation site lacrimation (1%).

## **9. Advisory Committee Meeting**

For this review cycle, this NDA did not raise issues which might benefit from discussion at 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**

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the originally proposed proprietary name, Xiidra, and granted conditional acceptance on April 29, 2015.

The Division of Risk Management (DRISK) completed a Risk Evaluation and Mitigation Strategy (REMS) review on June 20, 2015. The DRISK and the Division concurred that, if the NDA were to be approved, a REMS would not be necessary.

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

The formal labeling review was deferred until additional data is submitted to support the proposed indication.

The applicant submitted their proposed prescribing information in Pregnancy and Lactation Labeling Rule format. Labeling recommendations were provided by the Division of Pediatric and Maternal Health.

## **13. Decision/Action/Risk Benefit Assessment**

Regulatory Action: Complete Response

Risk Benefit Assessment: As the studies submitted failed their primary efficacy endpoints, there is a lack of substantial evidence consisting of adequate and well-controlled investigations 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. In addition, due to the product quality deficiencies, 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, and 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. Thus, the benefit of LIF for the treatment of the signs and symptoms of dry eye disease has not been established, and there is insufficient information that the product is safe for its intended use.

The Deputy Division Director Review and the Complete Response Letter detail the deficiencies and recommendations to address these deficiencies. An additional adequate and well controlled trial is recommended to provide substantial evidence of efficacy. Recommendations regarding the additional information needed and modifications to address the product quality deficiencies are also provided.

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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.**  
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/s/  
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JOHN J FARLEY  
10/16/2015

## Cross-Discipline Team Leader Review

<b>Date</b>	September 28, 2015
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA</b>	208073
<b>Applicant</b>	Shire Development, LLC.
<b>Date of Submission</b>	February 25, 2015
<b>PDUFA Goal Date</b>	October 25, 2015
<b>Proprietary Name / Established (USAN) names</b>	Xiidra (lifitegrast ophthalmic solution) 5%
<b>Dosage forms / Strength</b>	Topical ophthalmic solution
<b>Proposed Indication(s)</b>	Treatment of the signs and symptoms of dry eye disease
<b>Recommended:</b>	Not 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  $\alpha$ L $\beta$ 2) formulated as a <sup>(b)(4)</sup> 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 is not an immunosuppressant. 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 as completed to that

date and proposed 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 in order to reach agreement 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 in a population of subjects who use artificial tears be conducted and submitted in support of a NDA. On April 17, 2013, the IND sponsor, SARCode Corporation, was acquired by Shire Development, LLC. Correspondence regarding the IND was to continue to be with SARCode Bioscience.

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.

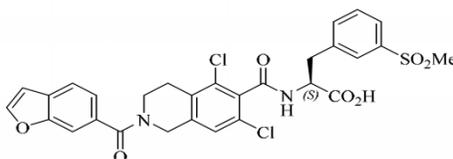
### 3. Product Quality

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<sub>29</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>7</sub>S

**Description and Composition of the Drug Substance:**

<b>Table 1: Lifitegrast Drug Substance (SSP-005493) Specifications</b>		
<b>Test</b>	<b>Acceptance Criteria</b>	<b>Analytical Procedure</b>
Description <sup>a</sup>	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 %, on (b) (4) <sup>a</sup> )	95.0 – 105.0% (w/w)	HPLC
Purity by HPLC (area %) <sup>a</sup>	≥96.0%	HPLC
Impurities by HPLC <sup>a</sup>		HPLC
(b) (4)	≤ (b) (4)%	
(b) (4)	≤ %	
Individual Unspecified Impurity (area %)	≤ %	
Total Impurities <sup>b</sup>	≤ %	
Chiral Purity by HPLC (area %)	≥ %	HPLC
(b) (4)	≤ %	(b) (4)
Residual Solvents by GC		
(b) (4)	NMT (b) (4) ppm	GC-FID

<b>Table 1: Lifitegrast Drug Substance (SSP-005493) Specifications</b>		
<b>Test</b>	<b>Acceptance Criteria</b>	<b>Analytical Procedure</b>
(b) (4)	NMT (b) (4) ppm	
	NMT (b) (4) ppm	GC-FID
	NMT (b) (4) ppm	GC-FID
Residue on Ignition	NMT (b) (4) %	USP <281>
Microbial Limit Tests		
Total Aerobic Plate Count	(b) (4) CFU/g	USP<61>
Total Yeast and Mold	(b) (4) CFU/g	USP<61>
Bacterial Endotoxins	(b) (4) EU/mg	USP<85>
(b) (4)		
(b) (4)	NMT (b) (4) ppm	USP <231>, Method II
	NMT (b) (4) ppm	(b) (4)

a Test required for reevaluation.

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

c Test to be performed on a minimum of 20 batches; further discussed in 3.2.S.4.5.

NMT = Not more than.

**Description and Composition of the Drug Product:**

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

<b>Table 2: Composition of the Drug Product Dosage Form</b>				
<b>Ingredient</b>	<b>Amount</b>	<b>Unit</b>	<b>Function</b>	<b>Reference to Standards</b>
<b>Drug substance(s)</b>				
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.
<b>Excipient(s)</b>				
Sodium Chloride	(b) (4)			USP/NF
Sodium Phosphate Dibasic, anhydrous				USP/NF
Sodium Thiosulfate, pentahydrate				USP/NF
Sodium Hydroxide, (b) (4)	(b) (4)		pH adjuster	USP/NF
(b) (4)	(b) (4)		(b) (4)	USP/NF

<b>Table 2: Composition of the Drug Product Dosage Form</b>				
<b>Ingredient</b>	<b>Amount</b>	<b>Unit</b>	<b>Function</b>	<b>Reference to Standards</b>
Hydrochloric Acid solution, (b) (4)	(b) (4)			USP/NF
Water for Injection				USP/NF
(b) (4)				

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

<b>Table 1: Specification for Lifitegrast 5.0% Ophthalmic Solution</b>		
<b>Test</b>	<b>Acceptance Criteria</b>	<b>Analytical Procedure</b>
Appearance <sup>a</sup>	Clear, colorless to slightly colored solution	Visual Inspection
Color <sup>a</sup>	(b) (4)	USP <631>
pH <sup>a</sup>	7.0–8.0	USP <791>
Osmolality <sup>a</sup>	200–330mOsm/kg	USP <785>
Lifitegrast Assay <sup>a</sup>	(b) (4) of Label Claim	HPLC-UV Detector
Degradation Products <sup>a</sup>		HPLC-UV Detector
Any Unidentified Degradation Product	Not More Than (b) (4) %	
Total Degradation Products	Not More Than %	
Identification A: HPLC Retention Time	The retention time of the major peak of the sample corresponds to the Lifitegrast peak in the reference standard solution.	HPLC-UV Detector
Identification B: UV Spectrum	The sample and reference HPLC peaks exhibit the same UV spectra from 200-400 nm.	HPLC-UV Diode Array
Minimum Fill Volume		USP <755>
Mean content	Not less than (b) (4) mL	
Content of any Single Container	Not less than mL	
(b) (4)	(b) (4) of Label Claim	HPLC-UV Detector
Particulate Matter (b) (4) <sup>a</sup>		USP <789>
	Not More Than (b) (4)	
	Not More Than	
Sterility <sup>a</sup>	No growth after (b) (4) days	USP <71>
Endotoxin <sup>a</sup>	Not more than (b) (4) EU/mL	USP <85>

<sup>a</sup> Tested on stability, as described in 3.2.P.8.

<sup>b</sup> 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”.

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 should be consistent 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) 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 of (b) (4) and that no individual (b) (4) contains less than (b) (4) of solution.

**Inspections:**

From the Quality Assessment addendum review dated 9/25/15:

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)	(b) (4)	<ul style="list-style-type: none"> <li>NME</li> <li>(b) (4) sole sourced from vendor currently in import alert.</li> </ul>	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) Mfg. and Release Testing	(b) (4)	(b) (4)	<ul style="list-style-type: none"> <li>NME</li> <li>(b) (4) Contract manufacturer where the stability sample storage, drug product storage, and incoming packaging material storage has not been previously inspected.</li> </ul>	Acceptable based upon PAI coverage
CTL - DP Release and Stability Testing			None	Acceptable based on manufacturing history
(b) (4) Secondary Packaging and Labeling			None	Acceptable based on manufacturing history

### Recommendation and Conclusion on Approvability

From the Quality Assessment addendum review dated 9/25/15:

This NDA is NOT recommended for approval from the CMC perspective.

The following items are considered for inclusion in the Complete Response Letter as approvability issues:

1. Regarding the response to the Agency Information Request dated June 2, 2015, the Agency believes that there is no adequate safety information to support the drug substance specification limit of (b) (4) ppm for (b) (4). Since no detectable levels of (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.”
2. The (b) (4) is not acceptable. Removal of the test for (b) (4) may be requested once adequate data is available.
3. In the leachable analysis in the stability study you have indicated that most of the impurities are degradants 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.

The following items, while not approvability issues, should be included in the Complete Response Letter:

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) does not appear to give (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 Comparability Protocol (b) (4) manufacturer and manufacturing process for both the drug substance and drug product included in the submission is not acceptable. It does not contain the provisions for commitments included in this current drug application. It should be withdrawn at this time
3. The reconciliation table submitted in your amendment dated 6/10/2015 (table 1 of question 10) is unclear, incomplete, and inaccurate. Consider the following recommendations when you revise the reconciliation table and/or submit any new tables.
  - 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).
- The reported (b) (4) is incorrect. It should be (b) (4).

#### 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  $\alpha$ L $\beta$ 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  $\mu$ L drop volume).

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. Although the exposure margins are low, the mild and transient nature of the findings observed does not present a major clinical concern. Eye irritation and eye pain were adverse reactions reported in the clinical trials with an incidence of 16% and 15%, respectively.

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 660-fold, indicating no clinical concern.

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. Based on AUC, the exposure margin for the fetal findings is 460-fold, indicating minimal clinical concern.

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 sternbrae 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, indicating minimal clinical concern.

The applicant will be asked<sup>1</sup> to reduce the specification for (b)(4), a potentially genotoxic impurity, to as low as reasonably possible. In addition, 3 leachables were found in developmental stability batch 3P80 and primary stability batches 4F14-2 and 4F90-2 at levels above (b)(4) ppm. The applicant will be asked<sup>2</sup> to identify these leachables and provide safety data to support these levels.

Approval is not recommended by Nonclinical Pharmacology/Toxicology, pending resolution of impurity issues cited above.

## 5. Clinical Pharmacology/Biopharmaceutics

From 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.

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<sup>1</sup> see CMC list of issues for communication to the applicant, Section 3 of this CDTL review

<sup>2</sup> see CMC list of issues for communication to the applicant, Section 3 of this CDTL review

### ***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. For the summary findings of this study, see Sections 4b and 5a of this NDA review.

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 ( $\geq 0.5$  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.

The Clinical Pharmacology recommends approval provided satisfactory agreement is reached between the applicant and the FDA regarding the language in Section 12 of the package insert.

## **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),  
(b) (4) and sealed (b) (4)  
(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.

## 7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 8/12/15:

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), OPUS-1 (Study 1118-KCS-200) and OPUS-2 (Study 1118-DRY-300) were all similar in design.

Phase 2 (Study 1118-KCS-100): The primary efficacy endpoint was the sign, inferior corneal staining score (0-4 point Ora scale), of the designated study eye at Day 84 (Week 12) without use of the CAE.

OPUS-1 (Study 1118-KCS-200): The primary analysis of the following co-primary endpoints was performed using a 2-sample t-test comparing lifitegrast to vehicle in the ITT Population with LOCF:

- Ocular Sign: Mean change from baseline to Day 84 (Visit 5) in inferior corneal fluorescein staining score (0-4 Ora scale)
- Ocular Symptom: Mean change from baseline to Day 84 (Visit 5) in the VR-OSDI (0-4 point mean composite score; Items 6-9).

OPUS-2 (Study 1118-DRY-300): The primary analysis of the following co-primary endpoints was performed using a stratified 2-sample t-test comparing lifitegrast to vehicle in the ITT Population with LOCF. The ANOVA model included treatment, strata, and the interaction between treatment and strata:

- Ocular Sign: Mean change from baseline to Day 84 (Visit 5) in inferior corneal fluorescein staining score (0-4 Ora scale)
- Ocular Symptom: Mean change from baseline to Day 84 (Visit 5) in eye dryness score (0-100 visual analogue scale, both eyes).

### Analysis of Primary Endpoint(s)

Phase 2 (Study 1118-KCS-100)

**Table 6.1.4-1**  
**Primary Efficacy – Inferior Corneal Staining Score at Day 84**  
**ITT Population**

	<b>0.1% LIF</b> N=57	<b>1% LIF</b> N=57	<b>5% LIF</b> N=58	<b>Vehicle</b> N=58
Baseline				
N	57	56	58	58
Mean (SD)	1.78 (0.473)	1.82 (0.508)	1.77 (0.515)	1.65 (0.513)
Day 84 (Week 12, Visit5)				
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) <sup>a</sup>	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	

<sup>a</sup> Analysis of covariance model with treatment, baseline, and site. P-value compared to vehicle from Dunnett's test. Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

Note: Results presented in this table are from the study eye only.

Source: CSR, Table 6

The trial did not meet its primary efficacy endpoint in this Phase 2 study. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 83 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.

OPUS-1 (Study 1118-KCS-200)

**Table 6.2.4-1**  
**Co-Primary Efficacy**  
**Inferior Corneal Staining Score at Day 84 (Sign)**  
**ITT Population with LOCF**

	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Baseline (Day 0)</b>		
n	294 <sup>a</sup>	293
mean (SD)	1.81 (0.599)	1.84 (0.597)
<b>Day 84 (Week 12, Visit 5)</b>		
n	294 <sup>a</sup>	293
mean (SD)	1.98 (0.874)	1.77 (0.879)
<b>Change from Baseline to Day 84</b>		
n	294	293
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

a 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: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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 1118-KCS-200, the lifitegrast treatment group achieved a statistically significant mean decrease from baseline to Day 84 in only one of the co-primary endpoints, inferior corneal fluorescein staining score.

OPUS-1 (Study 1118-KCS-200)

**Table 6.2.4-3**  
**Co-Primary Efficacy**  
**Visual-related Function Ocular Surface Disease Index (VR-OSDI) Subscale Score**  
**(Symptom)**  
**ITT Population with LOCF**

	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Baseline (Day 0)</b>		
N	295	293
mean (SD)	0.93 (0.958)	0.86 (0.931)
<b>Day 84 (Week 12, Visit 5)</b>		
N	295	292
mean (SD)	0.80 (0.838)	0.75 (0.861)
<b>Change from Baseline to Day 84</b>		
N	294	293
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: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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 other co-primary efficacy endpoint, visual-related function ocular surface disease index subscale score, was not statistically significant.

OPUS-2 (Study 1118-DRY-300)

**Table 6.3.4-1**  
**Co-Primary Efficacy**  
**Inferior Corneal Staining Score (Sign)**  
**ITT Population with LOCF**

	<b>Vehicle N=360</b>	<b>5% LIF N=358</b>
<b>Baseline (Day 0)</b>		
N	360	358
mean (SD)	2.40 (0.72)	2.39 (0.76)
<b>Day 84 (Week 12, Visit 5)</b>		
N	360	358
mean (SD)	1.69 (1.01)	1.66 (1.04)
<b>Change from Baseline to Day 84</b>		
N	360	358
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

a ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. Note: Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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.

In Study 1118-DRY-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.

OPUS-2 (Study 1118-DRY-300)

**Table 6.3.4-3**  
**Co-Primary Efficacy**  
**Eye Dryness Score (Visual Analogue Scale, Symptom)**  
**ITT Population with LOCF**

	<b>Vehicle N=360</b>	<b>5% LIF N=358</b>
<b>Baseline (Day 0)</b>		
N	360	358
mean (SD)	69.22 (16.76)	69.68 (16.95)
<b>Day 84 (Week 12, Visit 5)</b>		
N	360	358
mean (SD)	46.47 (29.87)	34.39 (27.86)
<b>Change from Baseline to Day 84</b>		
N	360	358
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

a ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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.

### 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 none of the submitted studies with efficacy evaluations were successful.

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 though there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.

The OPUS-1 study which was designed based on posthoc 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).

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).

## 8. 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 All Dry Eye Studies Pool was used for the presentation of exposure and overall safety results. 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

**Table 7.2.1-1**  
**Summary of Treatment Exposure – 12-Week Dry Eye Studies Pool<sup>c</sup>**  
**Safety Population**

	<b>Vehicle N=712</b>	<b>All LIF N=710</b>
Total duration of treatment exposure (days) <sup>a</sup>		
Mean (SD)	81.8 (12.46)	79.0 (18.04)
Standard error	0.47	0.68

	<b>Vehicle N=712</b>	<b>All LIF N=710</b>
Median	85.0	85.0
Min, max	1, 132	1,95
Subjects with duration of treatment exposure, n (%) <sup>b</sup>		
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

a Total treatment exposure is from first randomized masked study treatment to last.

b One month is 30.4375 days. The last category of at least 12 months is defined as at least 355 days based on the planned visit at Day 360 with a visit window of 5 days for SONATA.

c 12 Week Dry Eye Studies Pool (Phase 2, OPUS-1, and OPUS-2 Studies)

**Table 7.2.1-3**  
**Summary of Treatment Exposure**  
**SONATA Study – Safety Population**

	<b>Vehicle N=111</b>	<b>5% LIF N=220</b>
Duration of treatment exposure (days), mean (SD) <sup>a</sup>	311.3 (114.29)	304.4 (112.50)
Duration of treatment exposure, n (%) <sup>b</sup>		
> 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

a Total treatment exposure is from first randomized masked study treatment to last randomized masked study treatment. b One month is 30.4375 (365.25/12) days. The last category of at least 12 months is defined as at least 355 days based on the planned visit at Day 360 (Month 12, Visit 7) with a visit window of 5 days.

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

## Disposition of Subjects

Phase 2 (Study 1118-KCS-100)

**Table 7.3.3-1**  
**Reasons for Discontinuation – Phase 2 Allergic Conjunctivitis Study**  
**Safety Population**

<b>Subject Disposition</b>	<b>0.1% LIF N=15 n (%)</b>	<b>1% LIF N=15 n (%)</b>	<b>5% LIF N=15 n (%)</b>	<b>Vehicle N=15 n (%)</b>
Randomized subjects	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)
Subjects who completed study	13 (86.7)	13 (86.7)	21 (80.0)	13 (86.7)
Subjects who discontinued from study	2 (13.3)	2 (13.3)	3 (20.0)	2 (13.3)
<i>Primary reason for withdrawal</i>				
Adverse Event	0	1 (6.7)	2 (13.3)	1 (6.7)
Erroneously enrolled or did not meet entry criteria	1 (6.7)	0	0	0
Non-compliance	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)

Source: CSR, Module 2.7.4, Table 9

Note: The Randomized Population, Safety Population, and ITT Population were identical for the Phase 2 allergic conjunctivitis study.

OPUS-1 (Study 1118-KCS-200)

<b>Table 3: Subject Disposition (All Randomized Subjects)</b>			
	<b>Placebo N=295 n (%)</b>	<b>Lifitegrast N=293 n (%)</b>	<b>Total N=588 n (%)</b>
Screened subjects			1016
Randomized subjects	295	293	588
Safety Population <sup>a</sup>	295 (100.0)	293 (100.0)	588 (100.0)
ITT Population <sup>a</sup>	295 (100.0)	293 (100.0)	588 (100.0)
Per-protocol Population <sup>a</sup>	265 (89.8)	246 (84.0)	511 (86.9)
Subjects who completed study (ITT Population)			
Yes	284 (96.3)	281 (95.9)	565 (96.1)
No	11 (3.7)	12 (4.1)	23 (3.9)
Reason for withdrawal (ITT Population)			
Adverse event <sup>b</sup>	3 (1.0)	10 (3.4)	13 (2.2)
Lost to follow-up	2 (0.7)	0	2 (0.3)
Non-compliance	2 (0.7)	0	2 (0.3)
Pregnancy	1 (0.3)	0	1 (0.2)
Other	3 (1.0)	2 (0.7)	5 (0.9)

<sup>a</sup> Percentages based on randomized subjects.

<sup>b</sup> These subjects had a reason for study withdrawal of adverse event. An additional subject in the placebo treatment group was withdrawn from treatment, but not the study, due to an adverse event (refer to Appendix 16.2, Listing 7.6 and Listing 1.4).

ITT=intent-to-treat

Source: Section 14, Table 1.1.1 and Table 1.1.2

OPUS-2 (Study 1118-DRY-300)

<b>Table 3: Subject Disposition</b>			
	<b>Placebo N=360 n (%)</b>	<b>Lifitegrast N=358 n (%)</b>	<b>Total N=718 n (%)</b>
Screened subjects <sup>a</sup>			1455
Number of subjects not starting Placebo Run-in Period			557
Number of subjects not randomized after Placebo Run-in Period			178
Number of subjects randomized			720
Excluded from data analysis because records represent second randomization for a subject			2
Included in data analysis			718
Randomized Population	360	358	718
Safety Population <sup>b, c</sup>	359 (99.7)	359 (100.3) <sup>c</sup>	718 (100.0)
ITT Population <sup>b</sup>	360 (100.0)	358 (100.0)	718 (100.0)
Subjects who completed study <sup>b</sup>	348 (96.7)	321 (89.7)	669 (93.2)
Subjects who withdrew from study <sup>b</sup>	12 (3.3)	37 (10.3)	49 (6.8)
Reason for withdrawal <sup>b</sup>			
Adverse event <sup>b</sup>	3 (0.8)	26 (7.3)	29 (4.0)
Lost to follow-up <sup>b</sup>	0	2 (0.6)	2 (0.3)
Non-compliance <sup>b</sup>	0	1 (0.3)	1 (0.1)
Other <sup>b</sup>	9 (2.5)	8 (2.2)	17 (2.4)

<sup>a</sup> The total screening count of 1455 subjects includes 1450 unique subjects.

<sup>b</sup> Percentages based on Randomized Population.

<sup>c</sup> Subjects are categorized by actual treatment received, even if randomized to the other treatment. Subject 78-006 was assigned to the placebo group, but received lifitegrast via an incorrect kit at Day 14 (Week 2, Visit 3) and was discontinued from the study. This subject was included in the lifitegrast group for the Safety Population, but in the placebo group for the Randomized and ITT Populations.

ITT=intent-to-treat

Source: Section 14, Table 1.1.1 and Table 1.1.2

SONATA (Study 1118-DRY-400)

**Table 7.2.1-4  
 Subject Disposition – SONATA Study**

<b>Subject Disposition</b>	<b>Vehicle N=111 n (%)</b>	<b>5% LIF N=221 n (%)</b>	<b>Total N=332 n (%)</b>
Screened subjects <sup>a</sup>			504
Randomized subjects	111	221	332
Safety Population <sup>b</sup>	111 (100.0)	220 (99.5)	331 (99.7)
Subjects who completed study <sup>b</sup>	92 (82.9)	170 (76.9)	262 (78.9)
Subjects who discontinued study <sup>b</sup>	19 (17.1)	51 (23.1)	70 (21.1)
<i>Reasons for Discontinuation <sup>b</sup></i>			
Adverse Event	9 (8.1)	27 (12.2)	36 (10.8)
Death	1 (0.9)	0	1 (0.3)
Lost to follow-up	6 (5.4)	11 (5.0)	17 (5.1)

<b>Subject Disposition</b>	<b>Vehicle N=111 n (%)</b>	<b>5% LIF N=221 n (%)</b>	<b>Total N=332 n (%)</b>
Non-compliance	2 (1.8)	1 (0.5)	3 (0.9)
Erroneously admitted <sup>c</sup>	0	1 (0.5)	1 (0.3)
Other	1 (0.9)	11 (5.0)	12 (3.6)

Source: SONATA CSR, Table 3

a Number may reflect multiple screenings for the same subject

b Percentages based on Randomized Population

c Subject 41-032 was randomized in error but did not receive investigational product and is not included in the Safety Population.

## Deaths

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.

<b>Cause of Death</b>	<b>Study</b>	<b>Patient ID</b>	<b>Treatment group</b>	<b>Duration of Exposure</b>	<b>Other Medical Conditions</b>
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 >1% in Either Treatment Group**  
**All Dry Eye Studies Pool <sup>a</sup> – Safety Population**

<b>System Organ Class Preferred Term</b>	<b>Vehicle N=823 n (%)</b>	<b>All LIF N=1044 n (%)</b>
<b>Ocular TEAEs</b>		
Subjects with $\geq 1$ ocular TEAE	187 (22.7)	493 (47.2)
Eye disorders	135 (16.4)	262 (25.1)
Visual acuity reduced	48 (5.8)	66 (6.3)
Vision blurred	10 (1.2)	33 (3.2)
Lacrimation increased	4 (0.5)	29 (2.8)
Eye irritation	5 (0.6)	25 (2.4)
Eye pain	6 (0.7)	23 (2.2)
Eye pruritus	8 (1.0)	19 (1.8)
Ocular hyperemia	6 (0.7)	17 (1.6)
Conjunctival hemorrhage	4 (0.5)	12 (1.1)
Conjunctival hyperemia	10 (1.2)	12 (1.1)
Dry eye	11 (1.3)	9 (0.9)
General disorders and administration site	55 (6.7)	308 (29.5)

System Organ Class Preferred Term	Vehicle N=823 n (%)	All LIF N=1044 n (%)
conditions		
Instillation site pain	25 (3.0)	139 (13.3)
Instillation site irritation	22 (2.7)	130 (12.5)
Instillation site reaction	8 (1.0)	113 (10.8)
Instillation site pruritus	7 (0.9)	34 (3.3)
Instillation site foreign body sensation	2 (0.2)	11 (1.1)
Instillation site lacrimation	2 (0.2)	11 (1.1)
<b>Non-ocular TEAEs</b>		
Subjects with ≥ 1 non-ocular TEAE	184 (22.4)	355 (34.0)
Infections and Infestations	80 (9.7)	87 (8.3)
Nasopharyngitis	32 (3.9)	32 (3.1)
Sinusitis	9 (1.1)	12 (1.1)
Urinary tract infection	8 (1.0)	8 (0.8)
Nervous system disorders	23 (2.8)	175 (16.8)
Dysgeusia	3 (0.4)	143 (13.7)
Headache	6 (0.7)	25 (2.4)

Source: CSR, Module 2.7.4 Table 28

a All Dry Eye Studies Pool includes the Phase 2 Dry Eye Study, OPUS-1, OPUS-2 and SONATA studies.

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.

The 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%).

The treatment emergent adverse reactions which occurred in between 1% and 5% of subjects and more frequently in the lifitegrast group compared to the vehicle group were: instillation site pruritus (3%), lacrimation increased (3%), vision blurred (3%), eye irritation (2%), eye pain (2%), eye pruritus (2%), headache (2%), ocular hyperemia (2%), conjunctival hemorrhage (1%), instillation site foreign body sensation (1%), and instillation site lacrimation (1%).

## Nonfatal Serious Adverse Events

12-Week Dry Eye Studies Pool (Phase 2 Dry Eye, OPUS-1, and OPUS-2 Studies)

**Table 7.3.2-1**  
**Serious Treatment Emergent Adverse Events – 12-Week Dry Eye Studies Pool**  
**Safety Population**

Study	Subject Number	Treatment Group	Preferred Term
Phase 2 dry eye	002-1174	Vehicle	Asthma
Phase 2 dry eye	002-1195	Lifitegrast 0.1%	Oxygen saturation decreased
Phase 2 dry eye	002-1199	Lifitegrast 0.1%	Hip fracture

Study	Subject Number	Treatment Group	Preferred Term
Phase 2 dry eye	001-1125	Lifitegrast 1%	Cardiac arrest
OPUS-1	15-15002	Vehicle	Intervertebral disc protrusion
OPUS-1	20-20057	Vehicle	Prostate cancer
OPUS-1	12-12044	Lifitegrast 5%	Abdominal pain, upper
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-1	15-15051	Lifitegrast 5%	Humerus fracture
OPUS-2	50-052	Vehicle	Cerebrovascular accident
OPUS-2	58-001	Vehicle	Bladder cancer
OPUS-2	65-183	Vehicle	Osteoarthritis
OPUS-2	66-031	Vehicle	Colitis ischemic
OPUS-2	63-071	Lifitegrast 5%	Vertigo
OPUS-2	65-145	Lifitegrast 5%	Renal cancer
OPUS-2	73-034	Lifitegrast 5%	Thyrototoxic crisis

Source: CSR, Module 2.7.4 Table 37

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.

Note: The Phase 2 dry eye study used MedDRA Version 11.0. The OPUS-1 and OPUS-2 studies used MedDRA Version 14.1.

Approximately one percent of subjects in the lifitegrast and vehicle treatment groups experienced a serious adverse event. No patterns or safety concerns were raised by the reported adverse events.

SONATA (Study 1118-DRY-400)

**Table 7.3.2-2**  
**Serious Treatment Emergent Adverse Events – SONATA Study**  
**Safety Population**

Subject Number	Treatment Group	Preferred Term
38-004	Vehicle	Arrhythmia
38-008	Vehicle	Spinal fracture
44-002	Vehicle	Intervertebral disc protrusion
45-002	Vehicle	Chronic obstructive pulmonary disease
45-004	Vehicle	Chest pain
45-014	Vehicle	Chronic obstructive pulmonary disease
32-008	Lifitegrast 5%	Hip fracture
38-014	Lifitegrast 5%	Myocardial infarction
39-002	Lifitegrast 5%	Syncope, atrioventricular block
41-020	Lifitegrast 5%	Rheumatoid arthritis
41-051	Lifitegrast 5%	Osteoarthritis
45-019	Lifitegrast 5%	Dysmenorrhea
45-026	Lifitegrast 5%	Colonic polyp
46-003	Lifitegrast 5%	Urinary tract infection, pneumonia

Subject Number	Treatment Group	Preferred Term
48-004	Lifitegrast 5%	Back pain, transient ischemic attack

Source: CSR, Module 2.7.4 Table 39

Note: The SONATA study used MedDRA Version 14.1.

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.

The serious adverse events reported were considered not related to the investigational product and common in the age group studied. 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.

## Safety Summary Statement

Adequate and well controlled studies (Phase 2 Dry Eye, OPUS-1, OPUS-2 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 most frequent 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 (14%), instillation site pain (13%), instillation site irritation (13%), instillation site reaction (11%), and visual acuity reduced (6%).

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 original Biostatistics review dated 7/22/15:

Support for the efficacy and safety of Xiidra for the treatment of signs and symptoms of DED was based on four completed studies: a Phase 2 dose-ranging (Phase 2) and two Phase 3 (OPUS-1 and OPUS-2) efficacy and safety studies, and a Phase 3 safety study (SONATA). The primary focus of this review was based on the Phase 2, OPUS-1, and OPUS-2 studies.

Table 2: Summary of Pivotal Studies Reviewed

Study ID/ Study Type	Study Design / Primary Study Objective	Dose, Route and Regimen/ # of Patients	Duration of Treatment / Primary endpoint	Study Population
1118-KCS-100 (Phase 2)  Efficacy and Safety	Phase 2, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by inferior corneal staining score (ICSS) measured without use of the CAE at Day 84	Lifitegrast (LIF) 0.1, 1.0, or 5% or placebo ophthalmic solution; single drop BID  LIF 0.1% (N = 57) LIF 1.0% (N = 57) LIF 5.0% (N = 58) Placebo (N = 58)  <b>Total (N= 230)</b>	12 Weeks (84 Days)  The study included a primary sign efficacy endpoint:  <b>Sign:</b> inferior corneal fluorescein staining score	<ul style="list-style-type: none"> <li>• Subjects at least 18 years of age with dry eye disease.</li> <li>• had a history of ATU within six months prior to the screening visit on Day -14</li> <li>• Subjects with mild-to-moderate symptom</li> </ul>
1118-KCS-200 (OPUS-1)  Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. /  To evaluate efficacy as assessed by change from baseline to Day 84 in ICSS and VR-OSDI and to evaluate safety and tolerability	Lifitegrast (LIF) 5% or Placebo ophthalmic solution; single drop BID  LIF 5% (N = 293) Placebo (N = 295)  <b>Total (N = 588)</b>	12 Weeks (84 Days)  The study included co-primary efficacy endpoints:  (i) <b>Sign:</b> inferior corneal fluorescein staining score and  (ii) <b>Symptom:</b> visual-related function Ocular Surface Disease Index subscale (VR_OSDI) score	<ul style="list-style-type: none"> <li>• Subjects at least 18 years of age with dry eye disease.</li> <li>• Had a history of ATU within six months prior to the screening visit on Day -14</li> <li>• Subjects with mild-to-moderate symptom</li> </ul>

Study ID/ Study Type	Study Design / Primary Study Objective	Dose, Route and Regimen/ # of Patients	Duration of Treatment / Primary endpoint	Study Population
1118-DRY-300 (OPUS-2)  Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. /  To evaluate efficacy as assessed by change from baseline to Day 84 in ICSS and eye dryness score, and to evaluate safety and tolerability	Lifitegrast (LIF) 5% or Placebo ophthalmic solution; single drop BID  LIF 5% (N = 358) Placebo (N = 360)  <b>Total (N = 718)</b>	12 Weeks (84 Days)  The study included co-primary efficacy endpoints:  (i) <b>Sign:</b> inferior corneal fluorescein staining score and (ii) <b>Symptom:</b> Eye Dryness Score (EDS) [0–100 point visual analogue scale (VAS) in both eyes]	<ul style="list-style-type: none"> <li>• Subjects at least 18 years of age with dry eye disease.</li> <li>• Had a history of ATU within 30 days prior to the screening visit on Day -14</li> <li>• Subjects with moderate-to-severe symptom (EDS <math>\geq</math>40)</li> </ul>
1118-DRY-400 (SONATA)  Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5% or placebo ophthalmic solution; single eye drop BID  LIF 5% (N = 221) Placebo (N = 111)  <b>Total (N = 332)</b>	360 days (1 year)  To evaluate safety as assessed by ocular and non-ocular adverse events	Subjects at least 18 years of age with dry eye disease.

Source: Applicant's Section 2.7.6 Synopsis of Individual Studies

Substantial evidence for the proposed indication of treatment of signs and symptoms of dry eye disease was not shown based on review of the Phase 2, OPUS-1, and OPUS-2 studies.

- The change in visual-related function OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study. Statistical superiority in improving clinical symptom (using VR\_OSDI score) at Day 84 was not demonstrated.
- The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2. Statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated.
- Statistical superiority in improving the clinical sign (as measured using inferior corneal staining score) was demonstrated in only OPUS-1 study. In the Phase 2 and OPUS-2 studies, LIF 5% did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

## REMS

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

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

**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 in 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.

Per the OSI review dated June 26, 2015:

The studies 1118-KCS-200 entitled, “A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy of a 5% Concentration of SAR 1118 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye (OPUS-1)”, and 1118–DRY–300 entitled, “A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Efficacy of a 5% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Currently Using Artificial Tears (OPUS-2)”, and 1118–DRY–400 entitled, “A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Safety of a 5% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye (SONATA)” were inspected in support of this application.

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

**RESULTS (by Site):**

<b>Name of CI, Location</b>	<b>Protocol #/ Site #/ # of Subjects (enrolled)</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
John Lonsdale, M.D. Central Maine Eye Care	1118-KCS- 200/ 12/	20-24 Apr 2015	NAI

181 Russell St. Lewiston, ME 04240	80		
Robert Smyth-Medina, M.D. North Valley Eye Medical Group 11550 Indian Hills Rd, Suite 341 Mission Hills, CA 91345	1118-DRY-300/ 65/ 49	20, 21 Apr 2015	NAI
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. 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 not recommended for approval for the treatment of the signs and symptoms of dry eye disease.

The application does not provide substantial evidence of efficacy. Adequate and well controlled studies (Phase 2 Dry Eye, OPUS-1, OPUS-2 and SONATA Studies) do support the safety of the product for the treatment of the signs and symptoms of dry eye disease.

A formal labeling review is deferred until additional data is submitted to support the proposed indication.

**13. 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:**

The application does not provide substantial evidence of efficacy for lifitegrast ophthalmic solution, 5%, in the treatment of dry eye disease because none of the submitted studies with efficacy evaluations were successful.

- 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).

Adequate and well controlled studies (Phase 2 Dry Eye, OPUS-1, OPUS-2 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 most frequent 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 (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) ppm of (b) (4) in the drug substance has not been submitted. Since no detectable levels of (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.”
- 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) is not acceptable. Removal of the test for (b) (4) may be requested once adequate data is available.
  - b) The USP specification for particulate matter in ophthalmic solutions has been revised. Your proposed acceptance criterion for particulate matter is not consistent with the current USP specification. You should revise your acceptance criteria to be consistent with the USP monograph identified in your proposed drug product specifications, USP<789>.
  - c) Impurities have been identified which are not being tracked. You have indicated that most of the impurities are degradents from the drug product but you have not provided 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.

- 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.

#### ADDITIONAL COMMENTS

We have the following 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) does not appear to give (b) (4) (b) (4). Thus, the HPLC method is not stability-indicating for all potential drug substance degradation pathways. Optimize the method (b) (4) (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)

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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.**  
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/s/  
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WILLIAM M BOYD  
10/05/2015

WILEY A CHAMBERS  
10/05/2015

## CLINICAL REVIEW

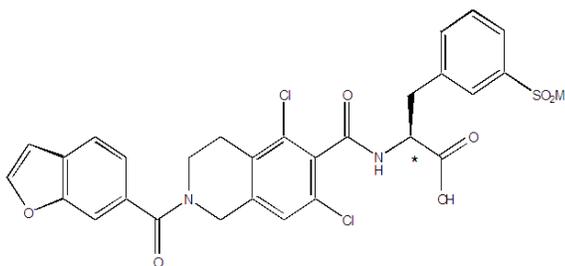
Application Type NDA  
Application Number(s) 208-073  
Priority or Standard Priority

Submit Date(s) February 25, 2015  
Received Date(s) February 25, 2015  
PDUFA Goal Date October 25, 2015  
Division / Office DTOP/OAP

Reviewer Name(s) Rhea A. Lloyd, MD  
Review Completion Date July 20, 2015

Established Name lifitegrast ophthalmic solution, 5%  
(Proposed) Trade Name Xiidra  
Therapeutic Class LFA-1 antagonist  
Applicant Shire Development, LLC.  
725 Chesterbrook Blvd.  
Wayne, PA 19087-5637  
866-744-7362

Formulation(s)



Dosing Regimen Instill 1 drop in the affected eye(s) twice a day

Indication(s) Treatment of the signs and symptoms of dry eye disease.

Intended Population(s) Adults with dry eye disease

Template Version: March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

NDA 208-073 is not recommended for approval from a clinical perspective.

The submitted studies were not successful in demonstrating effectiveness in the treatment of dry eye disease and thus did not demonstrate safety and efficacy for the proposed indication.

A formal labeling review is deferred until additional data is submitted to support the proposed indication.

Reviewer's Comments are in italics.

## 1.2 Risk Benefit Assessment

*The application supports 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. Adverse reactions most frequently associated with lifitegrast ophthalmic solution in this application were dysgeusia, instillation site pain, instillation site irritation, instillation site reaction, visual acuity reduced, instillation site pruritus, lacrimation increased, vision blurred, eye irritation, eye pain, eye pruritus, headache, ocular hyperemia, conjunctival hemorrhage, instillation site foreign body sensation and instillation site lacrimation.*

*The application does not support the efficacy of Xiidra (lifitegrast ophthalmic solution) 5% in the treatment of dry eye disease because none of the submitted studies with efficacy evaluations were successful.*

*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 though there were increasing numerical improvements in the inferior corneal staining score with higher lifitegrast doses.*

*The OPUS-1 study which was designed based on posthoc 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).*

*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).*

*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 previous safety and efficacy studies.*

*In summary, the application has demonstrated the safety of Xiidra (lifitegrast ophthalmic solution) 5%; however, none of the submitted studies supported its efficacy. Findings from the Phase 2 Dry Eye, OPUS-1, OPUS-2 and SONATA studies did not provide adequate evidence of efficacy for lifitegrast ophthalmic solution 5% in the twice daily dosing regimen for the treatment of dry eye disease.*

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Lifitegrast ophthalmic solution 5% is an antagonist of LFA-1 (also known as CD11a/CD18 or  $\alpha$ L $\beta$ 2) formulated as an unpreserved (b) (4) sterile eye drop. Lifitegrast binds to LFA-1 targets T-cell surface antigen and prevents interaction with its cognate ligand, ICAM-1 (also known as CD54). Lifitegrast is not an immunosuppressant.

Lifitegrast (formerly SAR1118, SSP-005493, and SPD606) is a sterile, clear colorless to pale yellow solution for ophthalmic use. The active ingredient is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl) propanoic acid.

Established Name:	lifitegrast ophthalmic solution 5%
Proposed Trade Name:	Xiidra
Chemical Class:	new molecular entity
Pharmacological Class:	LFA-1 antagonist
Indication:	treatment of the signs and symptoms of dry eye disease

Dosing Regimen: Instill 1 drop twice a day in the affected eye(s) using a single (b) (4) .  
 Age Groups: Adults with dry eye disease

**Table 2.1-1 Composition of Lifitegrast Ophthalmic Solution**

Component	Concentration % w/v	Function	Reference to Quality Standards
Lifitegrast	5.0	Active ingredient	(b) (4) CoA standards
Sodium Chloride	(b) (4)	(b) (4)	USP/NF
Sodium Phosphate Dibasic, anhydrous	(b) (4)	(b) (4)	USP/NF
Sodium Thiosulfate, pentahydrate	(b) (4)	(b) (4)	USP/NF
Sodium Hydroxide, (b) (4)	(b) (4)	pH adjuster	USP/NF
(b) (4)	(b) (4)	(b) (4)	USP/NF
Hydrochloric Acid solution, (b) (4)	(b) (4)	(b) (4)	USP/NF
Water for Injection	(b) (4)	(b) (4)	USP/NF

a Alternate concentrations may be used with appropriate adjustments to quantities

## 2.2 Tables of Currently Available Treatments for Proposed Indications

There are no ophthalmic drug products approved for the treatment of dry eye disease.

## 2.3 Availability of Proposed Active Ingredient in the United States

Lifitegrast is a new molecular entity that has not been approved in the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs

None.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Lifitegrast ophthalmic solution has been studied under IND 77885 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 as completed to that date and proposed 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 in order to reach agreement regarding the adequacy of the completed lifitegrast clinical efficacy studies to support a planned New Drug Application. The Agency confirmed that at least one additional trial utilizing the final formulation which confirmed efficacy for the objective endpoint of inferior corneal staining and a pre-specified subjective symptom in a population of subjects who use artificial tears would be expected in support of a NDA.

On April 17, 2013, the IND sponsor, SARCode Corporation, was acquired by Shire Development, LLC. Correspondence regarding the IND was to continue to be with SARCode Bioscience.

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 would 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.

## **2.6 Other Relevant Background Information**

None.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

*There is no evidence that the studies reviewed in this supplement were not conducted in accordance with acceptable clinical ethical standards. The results of the clinical inspections were pending at the time of this review.*

#### **3.2 Compliance with Good Clinical Practices**

The studies performed under IND 77,885 [Phase 2 Dry Eye Study(Study 1118-KCS-100) OPUS-1 (Study 1118-KCS-200), OPUS-2 (Study 1118-DRY-300) and SONATA (Study 1118-DRY-400)] were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki.

Before initiation of the studies, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The study began after receiving written approval from each EC/IRB.

#### **3.3 Financial Disclosures**

Shire has determined there were no financial interests or arrangements to disclose from investigators in clinical studies – Phase 2 Dry Eye, OPUS-1, OPUS-2 and SONATA. Shire Development, LLC. took the following steps to minimize potential bias of clinical study results by any of the investigators:

- Studies 1118-KCS-100, 1118-KCS-200, and 1118-DRY-300 included in this submission are double-blind randomized trials. The actual treatment given to individual subjects was determined by a randomization schedule. Per protocol, neither the randomization code nor the randomization sequence in these trials was to be broken except in emergency situations.
- All trial protocols were reviewed and approved by the Institutional Review Board (IRBs) before study initiation in order to ensure that the financial interests of the trial investigators did not compromise the protection of research subjects.
- The clinical trials were monitored by an external contract research organization according to the principles of Good Clinical Practice.

See Section 9.4 of this review.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Lifitegrast ophthalmic solution 5% is a sterile solution contained in unit-dose (b) (4) to be administered topically to the eye. It is contained in (b) (4) (b) (4) low-density polyethylene. A card of 5 (b) (4) is packaged in aluminum foil laminate pouches. Multiple foil pouches are packaged in a paperboard carton.

The formulation is a non-preserved, isotonic unit-dose ophthalmic. The formulation is adjusted to a pH of 7.0 – 8.0 with sodium hydroxide and/or hydrochloric acid.

**Table 4.1-1  
Regulatory Acceptance Specifications for Lifitegrast Ophthalmic Solution, 5%**

Test	Acceptance Criteria	Analytical Procedure
Appearance <sup>a</sup>	Clear, colorless to slightly colored solution	Visual Inspection
Color <sup>a</sup>	< (b) (4)	USP <631>
pH <sup>a</sup>	7.0 – 8.0	USP <791>
Osmolality <sup>a</sup>	200-330 mOsm/kg	USP <785>
Lifitegrast Assay <sup>a</sup>	(b) (4) of Label Claim	HPLC-UV Detector
Degradation Products <sup>a</sup>		HPLC-UV Detector
Any individual, Unspecified Impurity	Not more than (b) (4) %	
Total Impurities	Not more than (b) (4) %	
Identification: HPLC Retention Time	The retention time of the major peak of the sample corresponds to the lifitegrast peak in the reference standard solution.	HPLC-UV Detector
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) <sup>a</sup>		USP <789>
	Not more than (b) (4)	
	Not more than (b) (4)	
Sterility <sup>a</sup>	No growth after (b) (4) days	USP <71>
Endotoxin <sup>a</sup>	Not more than (b) (4) U/mL	USP <85>

<sup>a</sup> Tested on stability; <sup>b</sup> The acceptance criterion is based upon analysis relative to (b) (4) reference solutions prepared as described in the current European Pharmacopeia, Section 2.2.2. “Degree of Coloration of Liquids”.

#### Reviewer’s Comment:

1. The specifications should include a specification for any individual unspecified, non-degradation product.

2. *The specifications should include a specification for particles (b) (4).*

## **4.2 Clinical Microbiology**

*There is no clinical microbiology review for this product. It is not an anti-infective.*

## **4.3 Preclinical Pharmacology/Toxicology**

*Refer to the Pharmacology Toxicology review for details.*

## **4.4 Clinical Pharmacology**

### **4.4.1 Mechanism of Action**

Lifitegrast binds with the integrin LFA-1 in a manner that inhibits its interaction with the cell surface glycoprotein ICAM-1. Inhibition of LFA-1/ICAM-1 interaction results in the diminished recruitment of leukocytes to sites of inflammation and reduces the activation of leukocytes resulting in a reduction of the expression of proinflammatory cytokines.

### **4.4.3 Pharmacokinetics**

The pharmacokinetics of lifitegrast were evaluated in Study SAR 1118-001. This was a Phase 1, randomized, double-masked, placebo-controlled, dose-escalation study conducted in 28 healthy volunteers. There were 4 cohorts with 7 subjects in each cohort. The 4 cohorts corresponded to each of the 4 escalating dose levels (0.1, 0.3, 1, and 5%) of lifitegrast. The 7 subjects in each cohort were randomly assigned in a 5:2 ratio to receive either lifitegrast or placebo. All subjects who enrolled completed the study.

The lifitegrast tear concentrations increased in a roughly dose-proportional manner over the 0.1-5% lifitegrast dose range, although the tear pharmacokinetic parameters exhibited high pharmacokinetic variability with the coefficient of variation ranging from 90.6-105.4% for tear  $C_{\max}$  and from 78.4-109.8% for tear  $AUC_{0-t}$  across the 4 doses. Allowing for the high tear pharmacokinetic variability, there were no obvious differences between twice-daily and 3 times daily dosing schedules in tear pharmacokinetic results, and there was no accumulation of lifitegrast in tears during the twice-daily and 3 times daily regimens (refer to Section 9 of the SAR 1118-001 CSR).

Lifitegrast dose strengths of 0.1, 0.3, 1, and 5% administered up to 3 times daily in healthy subjects produced limited plasma exposure to lifitegrast, with measureable plasma concentrations only occurring with the 2 highest doses (lifitegrast 1 and 5%). The lifitegrast plasma concentrations appeared early, with mean  $t_{\max}$  ranging from 0.08-0.22 hours (5-13 minutes), and typically decreased rapidly to below measureable levels by 1 hour after

administration. The overall plasma pharmacokinetic profile demonstrated no systemic accumulation of lifitegrast with twice-daily or 3-times-daily administration over 10 days.

Additional pharmacokinetic analysis from the Clinical Pharmacology review:

Note that the single dose and multiple dose PK parameters generated in the Phase 1 trial were for a prototype formulation of lifitegrast ophthalmic solution. Briefly, in 5 healthy subjects treated twice daily for 10 days with lifitegrast 5.0% ophthalmic solution, the mean  $\pm$  SD (range) plasma lifitegrast  $C_{\max}$  was  $1.70 \pm 1.36$  ( $\leq 0.5 - 3.71$ ) ng/mL, achieved within 15 minutes post-dose. Plasma lifitegrast concentrations were below the LLOQ (0.5 ng/mL) of the PK assay after the 1 hour timepoint. On Day 10, both the mean plasma  $C_{\max}$  and AUC were approximately 3.5-fold higher than those measured on Day 1 of BID dosing. On Day 10, tear fluid lifitegrast concentrations in all these 5 healthy subjects were  $\geq 11.8$  ng/mL and  $\geq 164$  ng/mL at 24-hour post-dose and 8-hour post-dose, respectively.

In Study 1118-DRY-400 (SONATA), trough concentration of lifitegrast in plasma was assessed at Days 0 (predose), 180, and 360 (Months 0, 6, and 12) in approximately 25% of subjects at selected participating sites. No formal pharmacokinetic profiling was conducted. There was no evidence of accumulation of lifitegrast in plasma over time; the mean trough concentration of lifitegrast in plasma was below the lower limit of quantification (0.500ng/mL) at Days 0, 180, and 360 (Months 0, 6, and 12) (refer to Section 9.2 of the SONATA CSR).

Additional pharmacokinetic analysis from the Clinical Pharmacology review:

In the Phase 3 SONATA trial, 43 to 47 patients treated with the proposed commercial lifitegrast 5% ophthalmic solution (1 drop twice daily) were included in the PK and PD substudy; lifitegrast trough concentrations were measured on Days 180 and 360, and lymphocyte (CD3, CD4, and CD8) counts were measured on Days 0 (pretreatment), 180 and 360. In the 9 patients with detectable ( $\geq 0.5$  ng/mL) plasma lifitegrast trough concentrations ( $C_{\text{trough}}$ ), there was no apparent trend suggesting a relationship of relatively high predose lifitegrast concentrations and/or potentially clinically important (PCI) abnormalities in whole blood lymphocyte counts, or with the incidence of non-ocular immune disorders or infections (Table 3). There were no reported systemic infections or overimmunosuppressive complications in 2 of the 9 patients with  $C_{\text{trough}} \geq 2.5$  ng/mL, as well as in the additional patient with treatment-emergent PCI lymphocyte counts (i.e.,  $CD8 < 220/\mu\text{L}$ ) measured on Day 180. Of the remaining 6 patients, 1 patient with a detectable  $C_{\text{trough}}$  on Day 360 was reported to have had single episodes of kidney infection and sinus infection lasting from days 170 -176 and days 264 – 268, respectively, suggesting the lack of a temporal relationship between detectable lifitegrast exposure and infectious adverse events in this particular patient.

Overall, these observations suggest that the systemic exposures to lifitegrast following repeated dosing with the proposed to-be-marketed eyedrops at the proposed clinical dosage are limited, and do not produce clinically significant systemic chronic

immunosuppression, even though the measured lifitegrast trough concentrations (and presumably, the peak concentrations) in some patients in the SONATA trial exceeded the EC<sub>50</sub> needed to inhibit T cell adhesion (3.69 nM = 2.5 ng/mL) *in vitro*.

**Table [4.4.3-1] - Plasma lifitegrast trough (predose) concentrations in 9 patients with detectable concentrations of Day 180 or Day 360 of topical ocular dosing with lifitegrast 5% ophthalmic solution 1 drop twice daily (Phase 3 SONATA trial PK and PD subset)**

Unique Subject Identifier	Actual Sampling Day	Pre-dose plasma lifitegrast concentration (ng/mL)
1118_DRY_400-38-010	365	0.858
1118_DRY_400-45-007	182	3.74 <sup>c</sup>
1118_DRY_400-45-018	180	0.676
1118_DRY_400-45-019	176	1.31
1118_DRY_400-45-020	184	1.07
1118_DRY_400-45-021 <sup>a</sup>	175	0.555
1118_DRY_400-45-022	189	1.98
1118_DRY_400-45-025	185	3.31 <sup>c</sup>
	358	1.17
1118_DRY_400-45-041 <sup>b</sup>	184	1.84

LLOQ of plasma PK assay = 0.5 ng/mL

<sup>a</sup> Patient 45-021 had consistently Potentially Clinically Important (PCI) abnormal CD8 counts < 220  $\mu$ L, i.e., at screening (pre-treatment) and at the Days 180 and 360 on-treatment visits, and no reported infectious/immunosuppressive complications during the 12-month study.

<sup>b</sup> Patient 45-041 had a PCI abnormal CD8 count <220/mcL at the Day 180 visit (271/ $\mu$ L at screening; N/A on Day 360) but no reported infectious/immunosuppressive complications during the 12-month study.

<sup>c</sup> lifitegrast trough concentrations above the EC<sub>50</sub> needed for 50% inhibition of T cell adhesion (2.5 ng/mL) *in vitro*.

Because lifitegrast shows minimal systemic exposure with no systemic accumulation, no further clinical pharmacology studies were conducted.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

**Summary of Completed Clinical Studies for Lifitegrast Ophthalmic Solution, 5%**

Study Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Phase 1</b>					
<b>Study 1118-001</b>  PK and Safety	<u>Primary:</u> To assess safety and tolerability  <u>Secondary:</u> To determine the PK profile in plasma and tears	Randomized, double-masked, vehicle-controlled dose-escalation study	Lifitegrast 0.1, 0.3, 1.0, 5% or vehicle ophthalmic solution  28 healthy subjects (28 males/ 0 females)	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
<b>Phase 2</b>					
<b>Study 1118-KCS-100</b>  Safety and Efficacy	<u>Primary:</u> To evaluate the efficacy assessed by ICSS at Day 84  <u>Secondary:</u> To evaluate subjective and objective efficacy measures with and without the CAE; To evaluate safety and tolerability	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)

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Study Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Phase 3</b>					
<b>Study 1118-KCS-200</b> (SPD606-301; OPUS-1)  Safety and Efficacy	<u>Primary:</u> To evaluate efficacy assessed by change from BL to Day 84 in ICSS and VR-OSDI  To evaluate safety and tolerability  <u>Secondary:</u> To evaluate efficacy assessed by STT (means at Days 14 and 84) and total OSDI score (mean changes from BL to Days 14 and 84)	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 Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Study 1118-DRY-300</b> (SPD606-302; OPUS-2)  Safety and Efficacy	<u>Primary:</u> To evaluate efficacy assessed by change from BL to Day 84 in ICSS and EDS To evaluate safety and tolerability  <u>Secondary:</u> To evaluate efficacy assessed by change from BL to Day 84 in total corneal staining score, nasal conjunctival lissamine green staining score, eye discomfort score, and ODS	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)
<b>Safety</b>					
<b>Study 1118-DRY-400</b> (SPD606-303; SONATA)  Safety	<u>Primary:</u> To evaluate safety as assessed by ocular and non-ocular adverse events  <u>Secondary:</u> To evaluate safety and tolerability	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

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Study Identifier	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
<b>Study 1118-ACJ-100</b>  (Phase 2 allergic conjunctivitis study)	<u>Primary:</u> To evaluate safety as assessed by signs and symptoms of allergic conjunctivitis  <u>Secondary:</u> To evaluate safety and tolerability	Phase 2, single center, randomized, prospective, double-masked, vehicle-controlled, parallel arm study	Lifitegrast 0.1, 1.0, or 5% or vehicle ophthalmic solution  60 subjects with dry eye disease (31 males/ 29 females)	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

**Reviewer’s Comment:** *The reference product will be referred to as ‘vehicle’ throughout this review since this term more accurately describes its composition than ‘placebo’.*

## 5.2 Review Strategy

*The submitted clinical study reports, clinical protocols and relevant literature reports were reviewed. Modules 1 and 5 of the submission were reviewed in depth.*

## 5.3 Discussion of Individual Studies/Clinical Trials

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), OPUS-1 (Study 1118-KCS-200) and OPUS-2 (Study 1118-DRY-300) were all similar in design.

One multicenter, randomized, double-masked, vehicle-controlled safety study, SONATA, was also conducted in adult subjects with dry eye disease (DED).

### 5.3.1 Phase 2 Dry Eye Study (1118-KCS-100)

#### **A Phase 2, Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy of Three Different Concentrations (0.1%, 1%, 5%) of SAR1118 Ophthalmic Solution in Subjects with Dry Eye Using the Controlled Adverse Environment (CAE) Model**

##### **Study Centers**

This study was performed at five investigational centers within the U. S.

Site No.	No. of Randomized Subjects	Principal Investigator Name, Address	Subinvestigators
01	89	Gail L. Torkildsen, MD Ora, Inc. 300 Brickstone Square, 3 <sup>rd</sup> Floor Andover, MA 01810	John Pietrantonio, OD Clifford Michaelson, MD Kathleen Horn, OD Terry Chin, MD Charles Leahy, OD H. Jerome Crampton, MD
02	57	John Lonsdale, MD Central Maine Eye Care 181 Russell Street Lewiston, ME 04240	Troy M. Avery, OD
03	24	Eugene McLaurin, MD Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	David Evans, OD

Site No.	No. of Randomized Subjects	Principal Investigator Name, Address	Subinvestigators
04	43	Thomas K. Mundorf, MD Mundorf Eye Care 1718 East 4 <sup>th</sup> Street, Suite 703 Charlotte, NC 28204	None
05	17	Joel Geffin, MD The Eye Care Group, PC 1201 West Main Street, Suite 200 Waterbury, CT 06708	None

**Source:** Module 5.3.5.1.1\1118-KCS-100\Section 16.1.4

### Study Objectives

#### Primary:

To evaluate the efficacy of 3 different concentrations (0.1, 1, and 5%) of lifitegrast compared to vehicle in the treatment of dry eye as assessed by inferior corneal staining measured without use of the CAE. Comparisons were made during 12 weeks of treatment with twice daily dosing.

#### Secondary:

- To evaluate subjective efficacy measures (symptoms) of 3 different concentrations (0.1, 1, 5%) of lifitegrast compared to vehicle in the treatment of dry eye with and without use of the CAE model.
- To evaluate objective efficacy measures (signs) of 3 different concentrations (0.1, 1, 5%) of lifitegrast compared to vehicle in the treatment of dry eye with and without use of the CAE model.
- To evaluate the safety and tolerability of lifitegrast in subjects with dry eye.

### Methodology

This was a Phase 2, multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel-arm study with conducted in the US. Two hundred and thirty subjects with dry eye were randomized to lifitegrast 0.1, 1, 5% or vehicle ophthalmic solution at Visit 2 (Day 0, Week 0) and were instructed to follow a twice daily dosing regimen for 12 weeks.

The study was conducted in 3 periods: screening, treatment, and follow-up observation. A total of 5 challenges with the CAE were scheduled during screening and treatment (1 CAE at each visit). Ocular assessments and subject self-assessments were conducted prior to, during, and following each CAE in both eyes.

The Screening Period consisted of 2 visits (Visits 1 and 2 [Days -14 and 0, Weeks -2 and 0]). Each visit included exposure to the CAE. Subjects had to have a positive response in at least 1 eye at Visit 1 (Day -14, Week -2) and replicate the response in the same eye at Visit 2 (Day 0, Week 0) to be considered for further study eligibility. A positive response was defined as meeting all of the following criteria in the same eye:

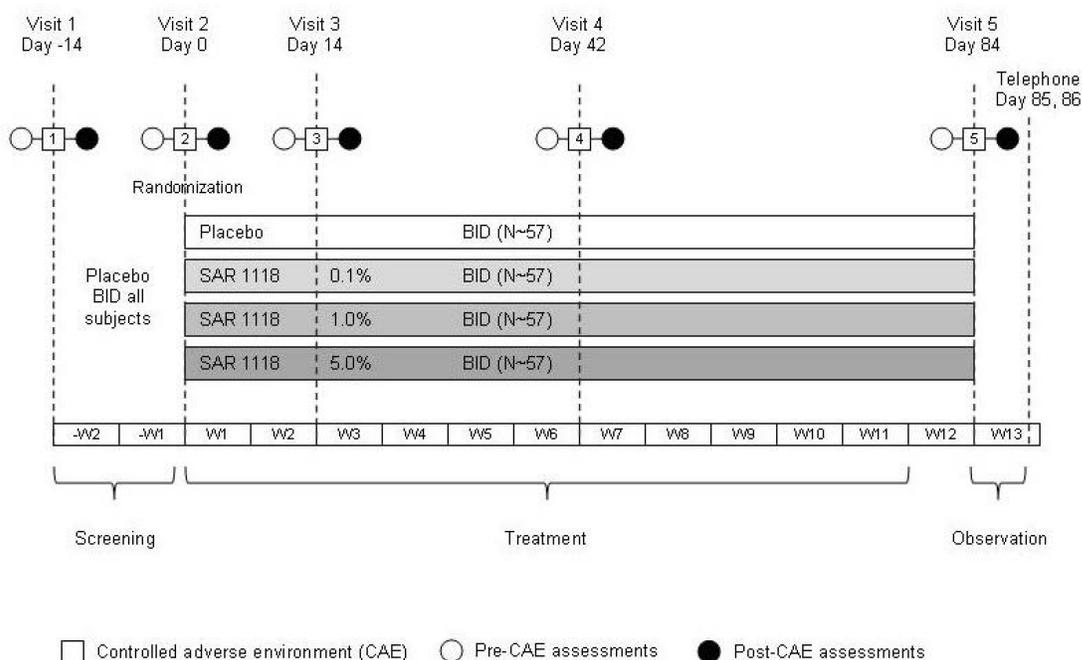
Lifitegrast ophthalmic solution, 5%

- Change from pre-CAE to post-CAE in inferior corneal fluorescein staining score  $\geq +1$
- Ocular Dryness Score (ODS)  $\geq 3$  at 2 consecutive time points (or score of 4 at 2 consecutive time points if the pre-CAE score = 3 at the same visit)
- Schirmer's Tear Test (STT) (without anesthesia)  $\geq 1$  and  $\leq 10$  mm.

The worst eye meeting these requirements was designated as the study eye.

The Treatment Period started at Visit 2 (Day 0, Week 0) and included Visits 3-5 (Days 14-84, Weeks 2-12). Site staff administered the first dose of randomized investigational product at Visit 2 (Day 0, Week 0) and at each scheduled visit. Subjects self-administered investigational product for all other doses until Visit 5 (Day 84, Week 12). Subjects were asked to rate and record ocular symptoms in daily diaries for 7 consecutive days prior to each visit. A follow-up telephone call was made approximately 2 days after the final treatment visit to assess concomitant medication use and AEs.

### Study Design Schematic



## Study Population

### Inclusion Criteria

Individuals eligible to participate in this study must have met all of the following criteria:

1. Willing and able to read, sign, and date the informed consent and Health Insurance Portability and Accountability Act (HIPAA) documents after the nature of the study had been explained and prior to initiation of Visit 1 (Day -14, Week -2) procedures or exams
2. Willing and able to comply with all study procedures
3. Be at least 18 years of age at the time of enrollment
4. Male or female
5. Use and/or desire to use artificial tear substitute for symptoms of dry eye within past 6 months
6. Best corrected visual acuity of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1 (Day -14, Week -2)
7. Subject-reported history of dry eye in both eyes
8. Corneal fluorescein staining score  $\geq 2$  (0-4 point Ora scale) in at least 1 eye pre-CAE at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0)
9. Conjunctival redness score  $\geq 1$  (0-4 point Ora scale) in at least 1 eye pre-CAE at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0)
10. A positive response in at least 1 eye, defined as meeting ALL of the following criteria in the same eye:
  - a. Change in inferior corneal fluorescein staining score  $\geq +1$  (0-4 point Ora scale, post-CAE value minus pre-CAE value at CAE 1 and 2)
  - b. ODS  $\geq 3$  at 2 consecutive time points (0-4 point Ora scale) during CAE 1 and 2 (or score of 4 at 2 consecutive time points if pre-CAE 1 and 2 score = 3 at the same visit)
  - c. STT (without anesthesia, pre-CAE 1 and 2)  $\geq 1$  and  $\leq 10$ mm  
If both eyes were equal, the right eye was selected.
11. A negative urine pregnancy test if female of childbearing potential (those who were not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must have used adequate birth control throughout the study. Adequate birth control was defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical-spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence may have been regarded as an adequate method of birth control.
12. Subjects with secondary Sjogren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosus) were eligible for enrollment consideration provided the subject met all other inclusion and exclusion criteria, AND, were not in a medical state – in the opinion of the principal investigator – that could have interfered with study parameters, were not taking systemic/ocular steroids, and were not immunodeficient / immunosuppressed (e.g., receiving immunosuppressive drugs to manage their baseline medical state).

### Exclusion Criteria

Individuals who met any of the following exclusion criteria were not eligible to participate in the study:

1. Contraindications to the use of the investigational products
2. Known hypersensitivity to the investigational product or its components
3. Pre-auricular lymphadenopathy or any ocular condition that, in the opinion of the investigator, could affect study parameters including, but not limited to, glaucoma, diabetic retinopathy, blepharitis, meibomian gland disease, follicular conjunctivitis, iritis, uveitis, and/or active ocular inflammation
4. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
5. Active or history of ocular herpes; and other ocular infection within the last 30 days
6. Unwilling to avoid wearing contact lenses for 7 days prior to and for duration of the study period
7. Positive urine pregnancy test
8. Any blood donation or significant loss of blood within 56 days of Visit 1 (Day -14, Week -2)
9. Any history of immunodeficiency disorder, human immunodeficiency virus, positive hepatitis B, C, or evidence of acute active hepatitis A (anti-hepatitis A virus immunoglobulin M) or organ or bone marrow transplant
10. Use of prohibited medications (topical, topical ophthalmic, systemic, and/or injectable) during the appropriate pre-study washout period and during the study. Prohibited medications included topical cyclosporine or use of any other ophthalmic medication (e.g., glaucoma medication, topical anti-inflammatory eye drops) for the duration of the study. The appropriate pre-study washout period was as follows:
  - a. Antihistamines (including ocular): 72 hours prior to Visit 1 (Day -14, Week -2)
  - b. Oral aspirin or aspirin-containing products allowed if dose had been stable over past 30 days prior to Visit 1 (Day -14, Week -2) and no change in dose anticipated during the study
  - c. Topical cyclosporine: 6 weeks prior to Visit 1 (Day -14, Week -2)
  - d. Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1 (Day -14, Week -2)
  - e. Any medication (oral or topical) known to cause ocular drying that had not been administered as a stable dose for at least 30 days prior to Visit 1 (Day -14, Week -2) and during the study
  - f. All other topical ophthalmic preparations (including artificial tear substitutes) other than the study drops: 72 hours prior to Visit 1 (Day -14, Week -2)
11. Any significant chronic illness that, in the opinion of the investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes
12. Use of any investigational product or device within 1 month prior to Visit 1 (Day -14, Week -2) or during the study period
13. History of laser-assisted in situ keratomileusis or similar type of corneal refractive surgery within 12 months prior to Visit 1 (Day -14, Week -2), and/or any other ocular

surgical procedure within 12 months prior to Visit 1 (Day -14, Week -2); or any scheduled ocular surgical procedure during the study period

14. Known history of alcohol and/or drug abuse within the past 12 months that, in the opinion of the principal investigator, may have interfered with study compliance, outcome measures including safety parameters, and/or the general medical condition of the subject.

**Reviewer’s Comment:**

*Minimum pre-CAE sign scores were required for study entry (e.g. Inclusion criteria 8 and 9); however, no minimum pre-CAE symptom score was required for study entry.*

**Removal of Subjects**

Subjects may have withdrawn their consent to participate in the study at any time without prejudice. The investigator must have withdrawn from the study any subject who requested to be withdrawn. In addition, a subject’s participation in the study may have been discontinued at any time at the discretion of the investigator and/or sponsor and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the Early Termination Visit should have been carried out.

Reasons for which the investigator or sponsor may have withdrawn a subject from the study included, but were not limited to the following:

- Subject experienced a serious or intolerable AE
- Subject required medication prohibited by the protocol
- Subject did not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or did not meet entry criteria
- Subject was lost to follow-up
- Subject became pregnant.

**Identity of Investigational and Reference Products**

Investigational product was supplied as a sterile, clear colorless liquid solution containing 0.1, 1, or 5% lifitegrast concentration in 4 cavity single dose, 0.5 mL low-density polyethylene unit dose (b) (4) with a fill volume of approximately (b) (4). The solution contained (b) (4), and (b) (4), and (b) (4). The lot numbers for 0.1, 1, and 5% lifitegrast were 03909C, 03909D, and 03909E, respectively.

The reference product consisted of all components of the investigational product solution with the exception of lifitegrast. The lot numbers for the reference product were 03909A and 03909B.

**Reviewer’s Comment:**

*The reference product is referred to as ‘Vehicle’ throughout this review since this term is a more accurate descriptor of its composition than ‘Vehicle’.*

## **Criteria for Evaluation**

### **Efficacy**

Efficacy was assessed by measures of ocular signs and symptoms. The ocular sign measurements included corneal fluorescein staining score, Schirmer Tear Test (STT), conjunctival lissamine green staining score, conjunctival redness score, tear film break-up time, blink rate, and ocular protection index. The ocular symptom measurements included Ocular Surface Disease Index (Allergan, Inc.) (OSDI), ODS, visual analogue scale (VAS), and 5-symptom assessment. Fluorophotometry and conjunctival impression cytology assessments were included as exploratory efficacy measurements.

### **Safety**

Safety was assessed by adverse events (ocular and non-ocular), BCVA, slit lamp biomicroscopy, dilated funduscopy, drop comfort, and corneal sensitivity.

## **Statistical Methods**

### **Determination of Sample Size**

The sample size calculation was based on Ora's experience with vehicle groups in similar CAE studies. The standard deviation of inferior corneal staining had been observed to be approximately 0.75. Assuming that the mean inferior corneal staining post-CAE at baseline was 3.0 units, a mean difference between treatment and vehicle of 0.45 units following treatment would amount to a 15% reduction in mean inferior corneal staining. Assuming a conservative standard deviation of 0.8 and using a 2-sided t-test at a significance level of 5%, 51 evaluable subjects per group were required to show a true mean difference of 0.45 units with 80% power under the assumption that the 3 active dose groups were autonomous and noncompeting, although they were being compared to the same control group. To account for approximately 10% of drop-outs, 57 subjects per group (approximately 228 subjects total) were to be enrolled in the study.

According to Rochon's chart of sample size calculation for repeated-measures experiments, the required sample size was less than 50 subjects per group to get 80% power for 3 times repeated-measures assuming an effect size= 0.45, standard deviation= 0.8, and correlation coefficients of 0.4 between 2 time points.

### **Evaluability**

#### **Intent to Treat Population:**

All randomized subjects (Efficacy analysis population)

#### **Per Protocol Population:**

All randomized subjects excluding those with any major protocol deviations or with incomplete efficacy data. Subjects to be excluded from the Per Protocol population were identified prior to database lock based on a masked review of protocol deviations by the clinical study team to determine whether they were considered major (i.e., having the potential to confound the interpretation of the safety or efficacy results).

### **Safety Population**

All randomized subjects who received at least 1 dose of investigational product.

### **Handling of Dropouts or Missing Data**

For the efficacy analysis, the LOCF method was used to impute missing values. Pre-treatment values were not imputed post-treatment; i.e., if observations immediately following treatment were missing, values prior to treatment were not carried forward and the assessment was treated as missing. If a baseline value was missing data, sensitivity analyses without imputation (completed subject analyses) were also performed.

### **Efficacy Analyses**

#### **Primary Efficacy Analysis**

The primary efficacy endpoint was the sign, inferior corneal staining score (0-4 point Ora scale), of the designated study eye at Day 84 (Week 12) without use of the CAE. The assumption was that the assessments of the 3 doses were autonomous and noncompeting, even though they were being compared to the same control. Therefore, the comparison-wise type I error rate and the per-pair power were controlled using an adjusted t-test. The primary efficacy analysis was a Day 84 assessment of pairwise treatment group differences (0.1% lifitegrast vs. vehicle, 1% lifitegrast vs. vehicle, and 5% lifitegrast vs. vehicle) that were analyzed at each time point by using an ANCOVA model with inferior corneal fluorescein staining score as the response. The ANCOVA model included treatment, study site, and baseline value of inferior corneal fluorescein staining as covariates; Dunnett's test was used to compare each concentration group of lifitegrast with vehicle. Statistically significant differences were defined as  $p < 0.05$ .

The primary efficacy endpoint was also analyzed for the difference between lifitegrast concentration (0.1, 1, and 5%) groups and vehicle using an unadjusted 2-sample t-test and a non-parametric Wilcoxon rank sum test, intended as supportive analyses. The change from baseline was analyzed using the same methods as well. Consistency amongst the results from the adjusted t-test, unadjusted t-test, and Wilcoxon rank sum test would suggest robust results.

No primary efficacy symptom was pre-specified in this study.

#### **Secondary Efficacy Analysis**

Secondary efficacy variables (all ocular signs and ocular symptoms defined in the criteria for evaluation) were analyzed using the same tests as the primary efficacy endpoint at each time point. Secondary endpoints were intended to be exploratory in nature, and hence no formal correction for multiplicity was performed.

### **Safety Analyses**

All safety analyses were performed on the Safety Population. For quantitative variables (i.e., BCVA and drop comfort), descriptive statistics including the mean, median, standard deviation, minimum, and maximum were summarized by visit and treatment. Qualitative variables (i.e., AE, dilated funduscopy, slit lamp findings) were summarized using counts and percentages by visit and treatment.

Adverse events were coded to system organ classes and preferred terms using the MedDRA (Version 11.0). A Treatment emergent adverse event (TEAE) was defined as any AE that occurred during the study, from the start of the investigational product dosing through the end of the study, or that worsened since the start of dosing. The number and percentage of subjects reporting any ocular and non-ocular TEAEs during the study was tabulated by system organ class and preferred term by treatment.

Study Schedule

Procedure	Visit 1 D-14 ± 2 CAE #1		Days -13 to -1	Visit 2 D0 CAE #2		Days 1-13	Visit 3 D14 ± 2 CAE #3		Days 15-41	Visit 4 D42 ± 4 CAE #4		Days 43-83	Visit 5 D84 ± 6 CAE #5		ET <sup>a</sup>	F/U <sup>b</sup> D85, 86
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		
Informed consent	X															
Demographic data (including height & weight)	X															
Medical history/medication history <sup>c</sup>	X															
Concomitant medication review				X			X			X			X		X	X
Inclusion/exclusion criteria <sup>d</sup>	X	X		X	X											
Urine pregnancy test <sup>e</sup>	X												X		X	
<b>Subjective Measures</b>																
ODS <sup>f</sup>	X	X		X	X		X	X		X	X		X	X	X	
5-symptom assessment	X	X		X	X		X	X		X	X		X	X	X	
VAS	X	X		X	X		X	X		X	X		X	X	X	
OSDI	X			X			X			X			X		X	
Drop comfort <sup>g</sup>					X											
<b>Objective Measures</b>																
BCVA	X			X			X			X			X		X	
Blink rate				X	X		X	X		X	X		X	X	X	
Slit lamp biomicroscopy	X	X		X	X		X	X		X	X		X	X	X	
Conjunctival redness score	X	X		X	X		X	X		X	X		X	X	X	
TFBUT	X	X		X	X		X	X		X	X		X	X	X	

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Procedure	Visit 1 D-14 ± 2 CAE #1		Days -13 to -1	Visit 2 D0 CAE #2		Days 1-13	Visit 3 D14 ± 2 CAE #3		Days 15-41	Visit 4 D42 ± 4 CAE #4		Days 43-83	Visit 5 D84 ± 6 CAE #5		ET <sup>a</sup>	F/U <sup>b</sup> D85, 86
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		
Corneal staining (fluorescein)	X	X		X	X		X	X		X	X		X	X	X	
Conjunctival staining (lissamine green)	X	X		X	X		X	X		X	X		X	X	X	
STT (without anesthesia)	X			X			X			X			X		X	
Dilated funduscopy		X												X	X	
Corneal sensitivity					X									X		
Fluorophotometry <sup>h</sup>				X									X			
CIC <sup>h</sup>														X		
<b>Study Therapy</b>																
Investigational product administration at study site <sup>i</sup>		X			X		X	X		X	X		X			
Placebo dispensation (open-label) <sup>i</sup>		X		X												
Placebo vial collection <sup>j</sup>				X											X	
Randomization <sup>k</sup>					X											
Investigational product dispensation <sup>i</sup>					X			X			X					
Investigational product collection <sup>l</sup>							X			X			X		X	
Diary dispensation <sup>l</sup>		X			X			X			X					
Diary collection <sup>l</sup>				X			X			X			X		X	
Diary completion at home <sup>m</sup>			X			X			X			X				

Procedure	Visit 1 D-14 ± 2 CAE #1		Days -13 to -1	Visit 2 D0 CAE #2		Days 1-13	Visit 3 D14 ± 2 CAE #3		Days 15-41	Visit 4 D42 ± 4 CAE #4		Days 43-83	Visit 5 D84 ± 6 CAE #5		ET <sup>a</sup>	F/U <sup>b</sup> D85, 86
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		
Investigational product administration at home <sup>1</sup>			X			X			X			X				
Telephone call to subject <sup>b</sup>																X
Adverse event assessment <sup>n</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study exit														X	X	

<sup>a</sup> Assessments that are normally collected pre- and post-CAE were only collected once at the Early Termination Visit. A follow-up phone call should have occurred within 1-2 days of early termination assessments.

<sup>b</sup> Follow-up phone call

<sup>c</sup> Significant non-ocular medical history only in the past year; medications taken only within the past 30 days

<sup>d</sup> Subjects must have replicated the following findings in the same eye on Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0) to be considered for further study eligibility: (1) change in inferior corneal fluorescein staining score  $\geq +1$ , (2) ODS  $\geq 3$  at 2 consecutive time points at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0), (3) STT without anesthesia  $\geq 1$  and  $\leq 10$ mm at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0). If both eyes were equal, the right eye was selected.

<sup>e</sup> Women of childbearing potential only

<sup>f</sup> Ocular discomfort score was obtained every 5 minutes during the 90-minute CAE exposure. The baseline value was obtained just prior to the CAE, and the post-CAE value was obtained after exit from the CAE. The CAE exposure was 90 minutes for all subjects at each visit.

<sup>g</sup> Drop comfort assessment was obtained in each eye immediately, then at 1, 2, and 3 minutes following instillation of the initial dose of investigational product (post-randomization).

<sup>h</sup> Exploratory measurements: approximately 10% of enrolled subjects underwent fluorophotometry (in the worst eye) and CIC at a single study site. Fluorophotometry was performed 30-60 minutes after the STT at Visits 2 and 5 (Days 0 and 84, Weeks 0 and 12). Conjunctival impression cytology was collected at the end of Visit 5 (Day 84, Week 12) before dilated funduscopy. Subjects waited at least 20 minutes from the end of the post-CAE evaluations until the CIC samples were collected. The worst eye was described by the ratings of the signs and symptoms of the ophthalmologic parameters as defined in the inclusion/exclusion criteria.

<sup>i</sup> At Visit 1 (Day -14, Week -2), subjects were administered open-label placebo drops in both eyes by trained study personnel 30 ± 5 minutes following the last post-CAE study assessment. Only a single dose of placebo drops was administered in both eyes on Day -14 (Visit 1, Week -2). At Visit 2 (Day 0, Week 0), following at least a 20-minute waiting period after pre-CAE ocular assessments, subjects were administered their first dose of open-label placebo for Day 0 (Visit 2, Week 0) by trained study personnel. At Visit 2 (Day 0, Week 0), following randomization, subjects were administered the first dose of investigational product 30 ± 5 minutes after the last post-CAE study assessment. Only a single dose of randomized

Procedure	Visit 1 D-14 ± 2 CAE #1		Days -13 to -1	Visit 2 D0 CAE #2		Days 1-13	Visit 3 D14 ± 2 CAE #3		Days 15-41	Visit 4 D42 ± 4 CAE #4		Days 43-83	Visit 5 D84 ± 6 CAE #5		ET <sup>a</sup>	F/U <sup>b</sup> D85, 86
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		Pre- CAE	Post- CAE		

investigational product was administered in both eyes on Day 0 (Visit 2, Week 0). Subjects then performed a drop comfort assessment immediately and then at 1, 2, and 3 minutes following initial dosing at Visit 2 (Day 0, Week 0) (post-randomization investigational product dosing). At Visits, 3, 4, and 5 (Days 14, 42, and 84, Weeks 2, 6, and 12), subjects received their first dose of the day by trained study personnel following at least a 20-minute waiting period after pre-CAE ocular assessments; the second dose of the day was administered by site personnel 30 ± 5 minutes after the last post-CAE study assessment (except on Visit 5 [Day 84, Week 12]).

<sup>j</sup> Placebo vials were collected at Visit 2 (Day 0, Week 0). Site staff confirmed that subjects had not administered their morning placebo dose at home for Visit 2 (Day 0, Week 0).

<sup>k</sup> All subjects who had a positive response (as defined previously) and met all other screening eligibility criteria after Visit 2 (Day 0, Week 0) were randomized to 1 of 4 treatment arms.

<sup>l</sup> Subject diaries and investigational product were dispensed at Visit 1 (Day -14, Week -2) (placebo vials and subject diaries) and, once randomized, at Visits 2, 3, and 4 (Days 0, 14, and 42, Weeks 0, 2, and 6). The investigational product and subject diaries were collected at the visit following the visit when they were dispensed. Upon drug return, site staff confirmed that subjects had not administered their morning dose at home for Visits 2, 3, 4, and 5 (Days 0, 14, 42, and 84, Weeks 0, 2, 6, and 12). Investigational product was self-administered by the subjects at home on Days -13 -- -1, Days 1-13, Days 15-41, and Days 43-83.

<sup>m</sup> Subjects recorded dosing information for the days they dosed at home. They rated and recorded ocular symptoms (5-symptom assessment) in their diaries daily for 7 consecutive days prior to their next study visit.

<sup>n</sup> Adverse event reporting began after each subject signed an informed consent form and continued through the observation period or follow-up phone call (Day 85 or 86).

BCVA=best corrected visual acuity, CAE=controlled adverse environment, CIC=conjunctival impression cytology, D=day, ET=early termination, F/U=follow-up, ODS=ocular discomfort score, OSDI=ocular surface disease index, STT=Schirmer tear test, TFBUT=tear film break-up time, VAS=visual analogue scale

**Reviewer's Comment:**

*Acceptable.*

### Changes in Study Conduct

The original protocol (Version 1.0, dated June 1, 2009) was amended once on September 8, 2009. In addition to minor editorial changes, the major changes included the following:

- The term “green” was added to conjunctival lissamine staining for consistency in wording.
- Language was added to clarify that only a single dose of vehicle drops was administered at Visit 1 (Day -14, Week -2). Twice daily dosing with vehicle began on Day -13.
- Language was added to clarify that fluorophotometry was performed on subjects in the worst eye, which was described by the ratings of the signs and symptoms of the ophthalmologic parameters as defined in the inclusion/exclusion criteria.
- Language was added to clarify that only a single dose of randomized investigational product was administered at Visit 2 (Day 0, Week 0). Twice daily dosing with randomized investigational product began on Day 1.
- Language was added to clarify that the same eye was evaluated on subjects for fluorophotometry at Visits 2 and 5 (Days 0 and 84, Weeks 0 and 12).
- Inclusion criterion 12 was added to clarify the eligibility of subjects with secondary Sjögren’s syndrome.
- Language was added to clarify exclusion criterion 14, such that subjects with a remote history of substance abuse who were disease free may have been considered for the study.
- The term “mean” was deleted from the primary efficacy endpoint.
- Language was added to the secondary efficacy endpoints to clarify the specific time points.
- Language was added to clarify the correct investigational product dosing time period for the initial dose at Visits 3, 4, and 5 (Days 14, 42, and 84, Weeks 2, 6, and 12) (i.e., at least 20 minutes after the pre-CAE ocular assessments).
- Language was added to clarify that site staff must have confirmed that subjects had not administered their morning dose at home for Visits 2, 3, 4, and 5 (Days 0, 14, 42, and 84; Weeks 0, 2, 6, and 12).
- Specific contact information for (b) (4) was deleted from the serious AE contact information.
- Lissamine staining was added to the pre-CAE assessments at Visit 4 (Day 42, Week 6).
- Language was added to describe the timing of the CAE at Visit 5 (Day 84, Week 12).
- Language (including an additional reference) was added to the sample size text to be consistent with the SAP.
- The study scheme figure was amended to include Week 9.

### Changes in the Planned Analyses

After completion of the study on February 18, 2010 and data unmasking, the data tables and listings were created by the contract research organization (b) (4) initially providing statistical support for this study. A clinical study report was prepared based on these data tables and listings. Analysis datasets and programming followed a (b) (4)

(b) (4) legacy process that was not consistent with Food and Drug Administration guidance or Clinical Data Interchange Standards Consortium conventions.

During a review of procedures followed by (b) (4) it was determined that SAS analysis datasets and documentation should be created following Clinical Data Interchange Standards Consortium Analysis Data Model Implementation Guide Version 1.0 to support all data tables and listings. The responsibility for creation of analysis datasets was transferred to a different statistical group (b) (4)

During the transition to an Analysis Data Model structure and creation of tables, issues were identified that required modifying the pre-specified analyses as described in the SAP. A combination of the data listings and tables created by (b) (4) and by the sponsor are presented in this updated clinical study report.

As these changes were introduced after unmasking, all of these changes are described in detail as follows:

#### Analysis method modifications:

- The SAP specified that the primary efficacy analysis was a Day 84 assessment of pairwise treatment group differences (0.1% lifitegrast vs. vehicle, 1% lifitegrast vs. vehicle, and 5% lifitegrast vs vehicle) that were to be analyzed across all time points by using ANCOVA accounting for repeated measures within each subject with inferior corneal fluorescein staining score as the response. The ANCOVA model included treatment, day, study site, and baseline value of inferior corneal fluorescein staining as covariates; an adjusted t-test was to be used.

In reviewing the programming code used for the repeated measures analyses, it was discovered that this produced a univariate regression analysis at each visit rather than a repeated measures analysis over Visits 3, 4, and 5 (Days 14, 42, and 84, Weeks 2, 6, and 12). The primary efficacy analysis of inferior corneal fluorescein staining at Day 84 has been analyzed by an ANCOVA model that includes treatment, study site, and baseline value of inferior corneal fluorescein staining as covariates. Dunnett's test has been used to compare each lifitegrast treatment group with vehicle.

- The Per Protocol population excluded subjects considered to have any major deviation, which included not completing the study. The primary efficacy analysis was performed on the Per Protocol population to assess the impact of the deviations. No further analysis was performed with only the completers.
- The following secondary efficacy variables are presented in listing. No hypothesis testing was done on these secondary efficacy variables.
  - Ocular discomfort score (intra-CAE)
  - 5-symptom assessment score (diary data)
  - Corneal staining scores (NEI scale)
  - Conjunctival staining score (NEI scale)

- The SAP specified that a 2-sample t-test was to be used to compare the average drop comfort of each lifitegrast concentration to vehicle. Descriptive statistics are presented for the drop comfort score; the 2-sample t-test was not performed.
- A post hoc analysis was performed with subjects who reported use of artificial tears within 30 days of Visit 1 (Day -14, Week -2) for corneal fluorescein staining.

### 5.3.2 OPUS-1 Study (1118-KCS-200; SPD606-301)

#### **A Phase 3, Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy of A 5% Concentration of SAR1118 Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye**

#### **Study Centers**

This study was performed at thirteen investigational centers within the U. S.

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
11	177	Gail L. Torkildsen, MD	Andover Eye Associates 138 Haverhill St. Andover, MA 01810  Ora, Inc. 138 Haverhill St. Andover, MA 01810
12	80	John Lonsdale, MD	Central Maine Eye Care 181 Russell Street Lewiston, ME 04240
13	74	Francis D'Ambrosio, MD	D'Ambrosio Eye Care 479 Old Union Turnpike Lancaster, MA 01523
14	9	C. Douglas Evans, MD	North Suburban Eye Associates 669 Main Street Wakefield, MA 01880
15	30	Joel Geffin, MD	The Eye Care Group, PC 1201 West Main Street, Suite 200 Waterbury, CT 06708

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
16	12	Linda Schumacher-Feero, MD	Atlee Gleaton Eye Care 227 Eastern Ave Augusta, ME 04330
17	11	Gerald Spindel, MD	Spindel Eye Associates Overlook Medical Park 6 Tsienneto Rd., Suite 101 Derry, NH 03038
18	27	Jack Greiner, DO	Charles River Eye Associates 955 Main Street, Suite 307 Winchester, MA 01890
20	66	Eugene McLaurin, MD	Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119
21	15	John Sheppard, MD	Virginia Eye Consultants 241 Corporate Blvd. Norfolk, VA 23502
23	49	Richard Eiferman, MD	Richard Eiferman, MD, PSD 6400 Dutchman's Parkway, Ste. 220 Louisville, KY 40405
28	23	Anthony Correnti, MD	NH Eye Associates, PA 1415 Elm Street Manchester, NH 03101
30	15	Steven Nielsen, MD	Nielsen Eye Center, Inc. 300 Congress Street Quincy, MA 02169

**Source:** Module 5.3.5.1.1\1118-KCS-200\ Section 16.1.4

## Study Objectives

### Primary:

- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by the co-primary endpoints of inferior corneal fluorescein staining (0-4 point Ora scale, ocular sign) and visual-related function Ocular Surface Disease Index subscale (VR-OSDI) score (0-4 point mean composite score; items 6-9 regarding reading, driving at night, use of computer and watching television) of the Ocular Surface Disease Index (OSDI [Allergan, Inc.]; ocular symptom), each measured by mean change from baseline to Day 84 (Visit 5).

- To evaluate the safety and tolerability of lifitegrast compared to vehicle in subjects with dry eye when administered twice daily for 12 weeks.

### **Secondary:**

#### **Ocular signs:**

- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by Schirmer Tear Test (STT; mm/5 minutes) measured by the mean at Day 14 (Visit 3)
- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 84 (Visit 5).

#### **Ocular Symptoms:**

- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 14 (Visit 3)
- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 84 (Visit 5).

### **Methodology:**

This was a Phase 3, multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel-arm study with block enrollment conducted in the US. Five hundred and eighty-eight subjects with dry eye disease were planned to be randomized in a 1:1 fashion to receive either lifitegrast 5% ophthalmic solution or vehicle ophthalmic solution at Visit 2. Subjects were instructed to follow a twice daily (morning and evening) dosing regimen for 12 weeks. The study was conducted in three periods: screening, treatment, and observation. The total duration of study participation was approximately 100 days (14 weeks).

### **Screening Period**

The Screening Period included 2 visits (Visits 1 and 2). Each visit included exposure to the Controlled Adverse Environment (CAE). Subjects had to have a positive response in at least 1 eye at Visit 1 and replicated the response in the same eye at Visit 2 in order to be considered for further study eligibility. A positive response was defined as meeting all of the following criteria in the same eye:

- Change from pre-CAE to post-CAE in inferior corneal fluorescein staining score  $\geq +1$
- ODS  $\geq 3$  at 2 consecutive time points (or score of 4 at 2 consecutive time points if the CAE Time 0 score = 3 at the same visit), and
- STT (without anesthesia)  $\geq 1$  and  $\leq 10$ mm.

The worst eye meeting these requirements was designated as the study eye.

### **Treatment Period**

Throughout the 12-week Treatment Period, subjects self-administered a single drop of investigational product twice daily (waking hours in morning and just prior to bedtime) in both eyes. Subjects were instructed to record AEs and investigational product dosing information in

their diary. Subjects were instructed not to administer their morning dose of investigational product before each study visit.

### **Observation Period**

A telephone safety assessment was conducted 1-2 days following the final assessments at Visit 5 or the early termination assessments.

### **Study Population**

#### **Inclusion Criteria**

To be eligible to participate in this study, subjects had to meet all of the following criteria:

1. Willing and able to read, sign, and date the informed consent and Health Insurance Portability Accountability Act documents after the nature of the study had been explained and prior to initiation of Visit 1 procedures or exams
2. Willing and able to comply with all study procedures
3. Was at least 18 years of age at the time of enrollment
4. Male or female
5. Use and/or desire to use artificial tear substitute for symptoms of dry eye within past 6 months
6. BCVA of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1
7. Subject-reported history of dry eye in both eyes
8. Corneal fluorescein staining score  $\geq 2$  [0-4 point Ora scale] in at least 1 region in at least 1 eye pre-CAE at Visits 1 and 2
9. Conjunctival redness score  $\geq 1$  [0-4 point Ora scale] in at least 1 region in at least 1 eye pre-CAE at Visits 1 and 2
10. A positive response when exposed to the CAE in at least 1 eye, defined as meeting ALL of the following criteria in the same eye:
  - a) Change in inferior corneal fluorescein staining score  $\geq +1$  (0-4 point Ora scale; post-CAE value minus pre-CAE value at CAE 1 and 2)
  - b) ODS  $\geq 3$  at 2 consecutive time points (0-4 point Ora scale) during CAE 1 and 2 (or score of 4 at 2 consecutive time points if the CAE 1 and 2 Time 0 score=3 at the same visit)
  - c) STT (without anesthesia, pre-CAE 1 and 2)  $\geq 1$  and  $\leq 10$  mm
11. A negative urine pregnancy test if female of childbearing potential (those who were not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must have used adequate birth control throughout the study. Adequate birth control was defined as hormonal – oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner. For non-sexually active females, abstinence was regarded as an adequate method of birth control.
12. Subjects with secondary Sjogren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosus) were eligible for enrollment consideration provided the subject met all other inclusion and exclusion criteria, AND, were not in a medical state – in the opinion of the principal investigator that could interfere with study parameters, were not taking

systemic/ocular steroids, and were not immunodeficient /immunosuppressed (e.g., receiving immunosuppressive drugs to manage their baseline medical state).

### **Exclusion Criteria**

Individuals were not eligible to participate in this study if they met any of the following criteria:

1. Contraindications to the use of the investigational product(s)
2. Known hypersensitivity to investigational product or its components
3. Received treatment with any concentration of lifitegrast ophthalmic solution in a previous clinical study
4. Pre-auricular lymphadenopathy or any ocular condition that, in the opinion of the investigator, could affect study parameters including, but not limited to, glaucoma, diabetic retinopathy, blepharitis, meibomian gland disease, follicular conjunctivitis, iritis, uveitis, and/or active ocular inflammation
5. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
6. Active or history of ocular herpes; any other ocular infection within the last 30 days
7. Unwilling to avoid wearing contact lenses for 7 days prior to and for duration of the study period
8. Positive urine pregnancy test or nursing an infant
9. Any blood donation or significant loss of blood within 56 days of Visit 1
10. Any history of immunodeficiency disorder, human immunodeficiency virus, positive hepatitis B, C, or evidence of acute active hepatitis A (anti-hepatitis A virus immunoglobulin M), or organ or bone marrow transplant
11. Use prohibited medications (topical, topical ophthalmic, systemic, and/or injectable) during the appropriate pre-study washout period (see below) and during the study. Prohibited medications included topical cyclosporine or use of any other ophthalmic medication (e.g., glaucoma medication, topical anti-inflammatory eye drops) for the duration of the study. The appropriate pre-study washout period was as follows:
  - a) Antihistamines (including ocular): 72 hours prior to Visit 1
  - b) Oral aspirin or aspirin-containing products allowed if dose was stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study
  - c) Topical cyclosporine: 6 weeks prior to Visit 1
  - d) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1
  - e) Any medication (oral or topical) known to cause ocular drying that had not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study; antihistamines were not allowed at any time during the study
  - f) All other topical ophthalmic preparations including artificial tear substitutes other than the study drops: 72 hours prior to Visit 1
12. Any significant chronic illness that, in the opinion of the investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes
13. Use of any investigational product or device within 30 days prior to Visit 1 or during the study period

14. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any scheduled ocular surgical procedure during the study period
15. Known history of alcohol and/or drug abuse within the past 12 months that, in the opinion of the principal investigator, may interfere with study compliance, outcome measures including safety parameters, and/or the general medical condition of the subject
16. Subjects with dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or destruction of conjunctival goblet cells (as with vitamin A deficiency) represent a specific, severely affected patient population and were not eligible for the study.

**Reviewer's Comment:**

*Minimum pre-CAE sign scores were required for study entry (e.g. Inclusion criteria 8 and 9); however, no minimum pre-CAE symptom score was required for study entry.*

**Removal of Subjects**

Subjects (or their legally authorized representative) had the right to withdraw consent for participation in the study at any time without prejudice. The investigator was to withdraw any subject who requested to be withdrawn from the study. A subject's participation in the study could have been discontinued at any time at the discretion of the investigator and/or sponsor and in accordance with his/her clinical judgment. However, investigators were encouraged to contact the sponsor, when possible, to discuss possible reasons for discontinuation prior to withdrawing a subject from the study. When possible, the tests and evaluations listed for the Early Termination Visit were carried out.

The sponsor reserved the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation of an individual investigator or site for poor enrollment or non-compliance.

Reasons for which the investigator or sponsor could have withdrawn a subject from the study included, but were not limited to, the following:

- Subject experienced a serious or intolerable AE
- Subject required medication prohibited by the protocol
- Subject did not adhere to study requirements specified in the protocol
- Subject was erroneously admitted into the study or did not meet entry criteria
- Subject was lost to follow-up
- Subject became pregnant.

If a subject failed to return for scheduled visits, documented efforts were made to determine the reason. If the subject could not be reached by telephone after 2 attempts, a certified letter was sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the investigator. Randomized subjects that were discontinued from the study were not replaced.

### **Administration of Investigational and Reference Products**

During the 2-week Screening Period, open-label vehicle was administered twice daily to the ocular surface of both eyes as an eye drop.

During the 12-week double-masked Treatment Period, subjects received twice daily doses of either vehicle or lifitegrast, administered to the ocular surface as an eye drop. On study visit days, the first dose of investigational product was instilled by study personnel; all other doses were instilled by the subject. Subjects were instructed to administer a single drop of investigational product twice daily (in the morning and just before bedtime in the evening) in both eyes.

### **Identity of Investigational and Reference Products**

Lifitegrast was supplied as a sterile, clear, colorless liquid solution containing 5% lifitegrast in 5 (b) (4) single dose, low-density polyethylene unit dose (b) (4) with a fill volume of approximately 0.2 mL. Each mL of a 5% solution contained 50 mg of lifitegrast. The lifitegrast solution contained the following excipients: (b) (4). The investigational product was packaged in masked kits. The lot number for lifitegrast was 1GC6. It was manufactured in July 2011 by (b) (4).

The vehicle was visually indistinguishable from the active solution. It consisted of all components of the lifitegrast solution with the exception of (b) (4). The lot number for the vehicle solution was 1GC5. The lot was manufactured in July 2011 by (b) (4).

### **Method of Assigning Subjects to Treatment Groups**

(b) (4) generated a stratified randomization list using a permuted block method in SAS Version 9.2. Subjects were randomly assigned to receive lifitegrast or vehicle based on a 1:1 ratio in the appropriate strata.

Randomization was centralized across sites and was stratified by the pre-CAE inferior fluorescein corneal staining score in the study eye at Visit 2 and by the prior use of artificial tears (defined as subjects who had routinely used over-the-counter artificial tears or topical ophthalmic lubricants until 72 hours before Visit 1). An Interactive Web Response System (IWRS) was used to facilitate subject randomization, accounting for the stratification factors. Upon a subject's qualification to enter the study, his/her Visit 2 pre-CAE inferior corneal staining score and prior active use of artificial tears was input into the IWRS system to classify the subject into 1 of the following strata:

- Visit 2 pre-CAE inferior corneal staining score  $\leq 1.0$  in the study eye and subject was not actively using artificial tears
- Visit 2 pre-CAE inferior corneal staining score  $\leq 1.0$  in the study eye and subject was actively using artificial tears
- Visit 2 pre-CAE inferior corneal staining score  $> 1.0$  in the study eye and subject was not actively using artificial tears

## **Criteria for Evaluation**

### **Efficacy**

Efficacy was assessed by measures of ocular signs and symptoms. The ocular sign measurements included corneal staining score (total, inferior, central, superior), blink rate, conjunctival redness score, tear film break-up time (TFBUT), lissamine staining score (cornea, conjunctiva), and STT. The ocular symptoms included OSDI score (symptoms, environmental triggers, and visual-related subscales), ODS, and visual analogue scale (VAS) (burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia, and pain).

### **Safety**

Safety was assessed by adverse events (ocular and non-ocular), best-corrected visual acuity (BCVA), slit lamp biomicroscopy, drop comfort assessment, intraocular pressure (IOP), corneal sensitivity, and dilated fundoscopy.

## **Statistical Methods**

### **Determination of Sample Size**

For the primary ocular sign, based on the results of the Phase 2 study, a 0.30 unit difference between lifitegrast and vehicle in the mean change from baseline to Day 84 (Visit 5) in inferior corneal staining, with a common SD of 0.95 units was expected. Under these assumptions, a sample size of 235 subjects per treatment group would yield approximately 93% power to show a significant difference at the  $\alpha=0.05$  level under a 2-sample t-test.

For the primary ocular symptom, based on the results of the Phase 2 study, it was reasonable to expect a 0.30 unit difference between lifitegrast and vehicle in the mean change from baseline to Day 84 (Visit 5) in the OSDI functional composite subscale, with a common SD of 0.95 unit. Under these assumptions, a sample size of 235 subjects per treatment group would yield approximately 93% power to show a significant difference at the  $\alpha=0.05$  level under a 2-sample t-test. This yielded an overall power of greater than 85% to show a difference in both sign and symptom (assuming independence).

To account for a potential 20% drop-out rate, it was planned to enroll 294 subjects per treatment group to maintain the stated power.

### **Evaluability**

#### **Safety Population:**

All randomized subjects who received at least 1 dose of investigational product.

#### **Intent-to-Treat Population:**

All randomized subjects who received at least 1 dose of investigational product.

#### **Per Protocol Population:**

All randomized subjects who completed the study with no major protocol violations. Sensitivity/robustness efficacy analyses were performed on the Per Protocol Population with observed data only.

### **Handling of Dropouts or Missing Data**

The method of last observation carried forward (LOCF) was used for the primary efficacy analysis on the ITT Population. In the case of missing data post-screening, post-challenge assessments were not carried forward. Additional imputation methods were used for the Per Protocol Population analyses. The worse observation carried forward (WOCF) (post-challenge assessments were not carried forward) and multiple imputation using Markov Chain Monte Carlo (MCMC) methods were applied to the ITT Population for the primary and secondary efficacy endpoints.

### **Efficacy Analyses**

#### **Primary Efficacy Analyses**

The primary analysis of the following co-primary endpoints was performed using a 2-sample t-test comparing lifitegrast to vehicle in the ITT Population with LOCF:

- Ocular Sign: Mean change from baseline to Day 84 (Visit 5) in inferior corneal fluorescein staining score (0-4 Ora scale)
- Ocular Symptom: Mean change from baseline to Day 84 (Visit 5) in the VR-OSDI (0-4 point mean composite score; Items 6-9).

The co-primary efficacy endpoints were also analyzed using additional statistical methods as pre-specified sensitivity analyses, including a non-parametric Wilcoxon rank sum test and a repeated-measures ANCOVA (adjusted for baseline and site) including data collected at Visits 3, 4, and 5 for confirmation. All analyses were also repeated for the ITT Population with WOCF and the Per-protocol Population with observed data only.

The primary analyses of the co-primary endpoints were based on 2-sample t-tests as specified in the protocol and the SAP; the stratification factors were not included as covariates in the analysis.

#### **Secondary Efficacy Analyses**

The following secondary efficacy endpoints were analyzed similarly to the co-primary efficacy endpoints:

##### Ocular Signs:

- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 14 (Visit 3)
- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by STT (mm/5 minutes) measured by the mean at Day 84 (Visit 5).

##### Ocular Symptoms:

- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 14 (Visit 3)

- To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye as assessed by the total OSDI score (0-100 scale) measured by mean change from baseline to Day 84 (Visit 5).

If both co-primary endpoints were significant, Simes modified Bonferroni procedure was applied to control the Type I error rate across the secondary endpoints within an analysis population.

P-values generated for other tests beyond those associated with the co-primary endpoint analyses and secondary endpoints that are under Type I error control are referred to as nominal p-values. These are descriptive and not inferential statistics.

Analyses were repeated for the ITT Population with WOCF and the Per Protocol Population with observed data only.

### **Safety Analyses**

All safety analyses were performed on the Safety Population. Descriptive analyses of the following safety variables were summarized by treatment group:

- Frequency and severity of TEAEs (overall, ocular, and non-ocular)
- BCVA
- Slit lamp biomicroscopy
- Drop comfort assessment upon instillation, and 1, 2, and 3 minutes post-instillation (Visits 2 – 5)
- Corneal sensitivity (Visits 1 and 5)
- IOP (Visits 1 and 5)
- Dilated funduscopy (Visits 1 and 5).

A 2-sample t-test was used to compare the average drop comfort rating of lifitegrast to vehicle

Study Schedule

Procedure	Visit 1 (Day -14 ± 3) CAE 1		Days -13 to -1	Visit 2 (Day 0) CAE 2			Days 1-13	Visit 3 (Day 14 ± 3)	Days 15-41	Visit 4 (Day 42 ± 4)	Days 43-83	Visit 5 (Day 84 ± 8)	ET/ UNS	F/U <sup>a</sup> (Day 85 or 86 ± 6)
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE	Post- random.								
Informed consent	X													
Demographic data	X													
Height and weight	X													
Medical history/medication history <sup>b</sup>	X													
Concomitant medication review				X				X		X		X	X	X
In/exclusion criteria <sup>c</sup>	X	X		X	X									
Urine pregnancy test <sup>d</sup>	X			X				X		X		X	X	
CAE exposure for 90min	X			X										
<b>Subjective Measures</b>														
ODS <sup>e</sup>	X	X		X	X			X		X		X	X	
VAS	X			X				X		X		X	X	
OSDI	X			X				X		X		X	X	
Drop comfort <sup>f</sup>							X	X		X		X		

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Procedure	Visit 1 (Day -14 ± 3) CAE 1		Days -13 to -1	Visit 2 (Day 0) CAE 2			Days 1-13	Visit 3 (Day 14 ± 3)	Days 15-41	Visit 4 (Day 42 ± 4)	Days 43-83	Visit 5 (Day 84 ± 8)	ET/ UNS	F/U <sup>a</sup> (Day 85 or 86 ± 6)
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE	Post- random.								
<b>Objective Measures</b>														
BCVA <sup>g</sup>	X			X				X		X		2X	X	
Blink rate				X				X		X		X	X	
Slit lamp biomicroscopy <sup>h</sup>	X	X		X	X			X		X		2X	X	
Conjunctival redness score	X	X		X	X			X		X		X	X	
TFBUT	X	X		X	X			X		X		X	X	
Corneal staining (fluorescein)	X	X		X	X			X		X		X	X	
Lissamine green staining <sup>i</sup>	X	X		X	X			X		X		X	X	
STT (without anesthesia)	X			X				X		X		X	X	
Corneal sensitivity <sup>j</sup>		X										X	X	
IOP <sup>j</sup>		X										X	X	
Dilated funduscopy <sup>j</sup>		X										X	X	
<b>Study Therapy</b>														
Open-label placebo administration at study site <sup>k</sup>		X		X	X									
Open-label placebo dispensation <sup>l</sup>		X												

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Procedure	Visit 1 (Day -14 ± 3) CAE 1		Days -13 to -1	Visit 2 (Day 0) CAE 2			Days 1-13	Visit 3 (Day 14 ± 3)	Days 15-41	Visit 4 (Day 42 ± 4)	Days 43-83	Visit 5 (Day 84 ± 8)	ET/ UNS	F/U <sup>a</sup> (Day 85 or 86 ± 6)
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE	Post- random.								
Open-label placebo administration at home <sup>l</sup>			X											
Placebo vial collection <sup>m</sup>				X									X	
Randomization <sup>n</sup>					X									
Investigational product administration at study site <sup>k</sup>						X		X		X		X		
Investigational product dispensation <sup>l</sup>						X		X		X				
Investigational product administration at home <sup>l</sup>							X	X	X	X	X			
Investigational product collection <sup>l</sup>								X		X		X	X	
Diary dispensation <sup>l</sup>		X				X		X		X				
Diary completion at home <sup>o</sup>			X				X		X		X			
Diary collection <sup>l</sup>				X				X		X		X	X	
Telephone call to subject <sup>a</sup>														X
AE assessment <sup>p</sup>	X	X	X	X	X		X	X	X	X	X	X	X	X
Study exit												X	X	

<sup>a</sup> Follow-up telephone call occurred within 1-2 days following final assessment at Visit 5 or 1 to 2 days following ET assessments.

<sup>b</sup> Only significant non-ocular medical history during the past year; only medications taken within the past 30 days.

<sup>c</sup> Subjects had to replicate the following findings in the same eye at Visits 1 and 2 in order to be considered for further study eligibility: (1) change in inferior corneal fluorescein staining

Procedure	Visit 1 (Day -14 ± 3) CAE 1		Days -13 to -1	Visit 2 (Day 0) CAE 2			Days 1-13	Visit 3 (Day 14 ± 3)	Days 15-41	Visit 4 (Day 42 ± 4)	Days 43-83	Visit 5 (Day 84 ± 8)	ET/ UNS	F/U <sup>a</sup> (Day 85 or 86 ± 6)
	Pre- CAE	Post- CAE		Pre- CAE	Post- CAE	Post- random.								

score  $\geq 1$ , (2) ODS  $\geq 3$  at 2 consecutive time points (or score of 4 if the CAE Time 0 score=3 at the same visit) at Visits 1 and 2, and (3) STT without anesthesia  $\geq 1$  and  $\leq 10$ mm at Visits 1 and 2. If both eyes met the 3 criteria above, the eye with the greatest increase in inferior corneal staining in the CAE at Visit 2 was selected as the study eye. If both eyes had an equal increase in inferior corneal staining at Visit 2, the eye with the lowest STT value at Visit 2 was designated as the study eye. If both eyes had equal changes in inferior corneal staining and equal STT values at Visit 2, the right eye was selected as the study eye.

<sup>d</sup> Women of childbearing potential only.

<sup>e</sup> Ocular discomfort self-assessment score was obtained just prior to entering, during, and just after the CAE exposure. During the CAE exposure, ODS was collected at Time 0 and every 5 minutes thereafter throughout the 90±5 minute exposure.

<sup>f</sup> Drop comfort assessments were obtained in each eye immediately, then at 1, 2, and 3 minutes following instillation of the investigational product. At Visits 2, 3, 4, and 5, drop comfort assessments were conducted following the initial dosing of the day. For all drop comfort assessments, subjects were administered investigational product by trained study personnel.

<sup>g</sup> A BCVA assessment was measured as a pre-CAE assessment at Visits 1 and 2 and prior to investigational product administration at Visits 3, 4, and 5. At Visit 5, a BCVA assessment was also measured after the final dose of investigational product was administered at the site by trained study personnel.

<sup>h</sup> A slit lamp examination was performed pre- and post-CAE at Visits 1 and 2 and prior to investigational product administration at Visits 3, 4, and 5. At Visit 5, a slit lamp examination was performed after the final dose of investigational product was administered at the site by trained study personnel.

<sup>i</sup> Lissamine staining scores evaluated both the cornea (inferior, superior, central regions) and conjunctiva (nasal and temporal regions). The total lissamine score represents the epithelial staining of the entire ocular surface.

<sup>j</sup> Corneal sensitivity, IOP, and dilated fundoscopy assessments were performed at the end of Visits 1 and 5.

<sup>k</sup> At Visit 1, after achieving a positive response as defined by the protocol, subjects self-administered a single dose of open-label placebo drops in both eyes, for training purposes, at the study site under the supervision of trained study personnel 30±5 minutes following the last post-CAE study assessment. Only a single dose of placebo drops was administered on Day -14 (Visit 1). At Visit 2, following a 20±5-minute waiting period after pre-CAE ocular examination assessments, subjects were administered their first dose of placebo drops in both eyes (open-label, single drop). Following the screening procedures at Visit 2, all subjects received their last dose of placebo drops in both eyes (open-label, 2 drops in each eye) at the study site by trained study personnel 20±5 minutes following the last post-CAE study assessment. At Visits 3, 4, and 5, subjects received their first dose of investigational product by trained study personnel following a 15±5 minute waiting period after the last study assessment.

<sup>l</sup> Open-label placebo vials and diaries were dispensed at Visit 1 and were self-administered by the subjects at home on Days -13 to -1. The open-label placebo vials and diaries were collected at Visit 2. Upon return of the open-label placebo vials, site staff confirmed subjects had NOT administered their morning dose at home for Visit 2. After randomization, randomized investigational product vials and diaries were dispensed at Visits 2, 3, and 4. The investigational product and diaries were collected at the next visit. Upon investigational product vial return, site staff confirmed subjects had NOT administered their morning dose at home for Visits 3, 4, and 5. Investigational product was self-administered by subjects at home on Days 1-13, Days 15-41, and Days 43-83.

<sup>m</sup> Placebo vials were collected at Visit 2. Site staff were to confirm subjects had NOT administered their morning placebo dose at home for Visit 2.

<sup>n</sup> All subjects who had a positive response and met all other screening eligibility criteria after Visit 2 were randomized to 1 of 2 treatment groups (lifitegrast or placebo).

<sup>o</sup> Subjects recorded placebo run-in and randomized investigational product dosing information for the days they self-dosed at home.

<sup>p</sup> Adverse event reporting began after each subject signed an informed consent form and continued through the follow-up telephone call 1-2 days post-Visit 5 (Day 85 or 86) or ET assessments.

AE=adverse event; BCVA=best corrected visual acuity; CAE=controlled adverse environment; ET=early termination; F/U=follow-up; IOP=intraocular pressure; ODS=ocular discomfort score; OSDI=Ocular Surface Disease Index; random.=randomization; STT=Schirmer Tear Test (unanesthetized); TFBUT=tear film break-up time; UNS=unscheduled visit; VAS=visual analogue scale.

### Changes in Study Conduct

The original protocol (Version 1.0, dated May 27, 2011) was amended once on August 5, 2011. In addition to minor editorial changes, the major changes included the following:

- The sponsor name was changed from SARcode Corporation to SARcode Bioscience, Inc.
- In the synopsis, the Screening Period window for Day -14 was changed from  $\pm 2$  days to  $\pm 3$  days to be consistent with the main text of the protocol.
- Language was added to clarify eligibility criteria for the ODS (measured over 2 consecutive time points during the same visit at Visits 1 and 2).
- Language was added to provide consistency throughout the protocol in the timing of the vehicle drops and randomized investigational product instillation.
- Language was added to clarify that women who are nursing infants were excluded from study participation.
- The schedule of events was revised to clarify the following items:
  - Added height and weight as a separate line item for Visit 1 since this information was captured separately from the demographic data in the eCRF.
  - Updated to reflect that 2 BCVA and slit lamp biomicroscopy assessments were performed at Visit 5 (1 pre- and 1 post-dose).
  - Added a mark to indicate the study exit procedure was completed at Visit 5.
  - Deleted language to clarify that the previous pre- and post-CAE comment for the Early Termination Visit no longer applied since CAEs were only conducted prior to randomization at Visits 1 and 2. The Early Termination Visit was amended to Early Termination Visit/Unscheduled Visit since all of the same assessments were conducted at unscheduled visits.
  - Added language to provide consistency for the timing of doses for all visits.
- Language was added to use the correct title of the study medication dosing log and to clarify dosing compliance.
- Language was added to clarify the definition of an SAE.
- Language was updated to include the drop comfort assessment at Visit 5 after investigational product instillation.
- Language was added to address how to conduct unscheduled visits and to clarify the process for subjects who were lost to follow-up.
- Appendix 3 (VAS) was revised to remove the VAS post-CAE at Visits 1 and 2 and to remove the wording that the VAS rating was recorded separately for each eye. The VAS was only conducted prior to the CAE at Visits 1 and 2 and ratings were recorded for both eyes.
- Appendix 6 (Sample Diary Pages) was revised for the Open-label Vehicle Diary and Randomized Study Drug Diary pages to reflect more accurate information and clarify at home dosing after Visits 1, 2, 3, and 4.
- Appendix 8 (Procedure for Evaluating Blink Rate) was revised to measure blink rate for 10 minutes instead of 3 minutes.

### Changes in the Planned Analyses

The secondary objectives and efficacy variables defined in the SAP differ from those listed in the study protocol. As the SAP was drafted, the list of secondary endpoints was further changed, and hence the secondary objectives and efficacy variables defined in the SAP supersede those listed in the protocol.

After data unmasking, the data tables and listings were created by the contract research organization (b)(4) initially providing statistical support for this study. Analysis datasets and programming followed an (b)(4) legacy process that was not consistent with Food and Drug Administration guidance or Clinical Data Interchange Standards Consortium conventions. The responsibility for statistical support was transferred to a different statistical group (b)(4) (b)(4). During a review of procedures followed by (b)(4), it was determined that SAS analysis data sets and documentation should be created following Clinical Data Interchange Standards Consortium Analysis Data Model Implementation Guide Version 1.0 to support all data tables and listings. During the transition to an Analysis Data Model structure, issues were identified that required modifying the (b)(4) analyses. This clinical study report was based upon these revised analyses.

The tables and listings produced by (b)(4) have been archived and can be provided for review, upon request. While there are numeric changes in the reported data, the overall inference and conclusions remain the same.

As these changes were introduced after unmasking, all of these changes are described in detail as follows:

- Analysis method changes:
  - Repeated Measures Supportive Analyses
    - The SAP specified that the supportive, repeated measures analyses for the co-primary and secondary efficacy analyses were to be provided using a number of data conventions: ITT with LOCF, WOCF, MCMC, and Per-protocol analysis with observed data and no imputation. These analyses were to be based upon data collected at Visits 3, 4, and 5. In reviewing the programming code used for the repeated measures analyses, it was discovered that this produced a univariate regression analysis at each visit rather than a repeated measures analysis over Visits 3, 4, and 5. The repeated measures analysis in the revised tables captures the basic structure of the model described above but produces an overall analysis by using revised code. As 1 of the primary reasons for using the repeated measures analysis was to investigate the effect of the missing data on the analyses, the repeated measures analysis was implemented using observed data only.
  - MCMC Imputation
    - The SAP specified that MCMC would be used as 1 of the confirmatory analyses to investigate the effect of missing data over time on the primary

analyses. As there were very few missing observations (e.g., the co-primary endpoint of inferior corneal fluorescein staining score was missing for 11 of 295 subjects receiving vehicle and 12 of 293 subjects receiving lifitegrast), it was decided not to perform the MCMC imputation and rely on the other confirmatory analyses (WOCF, Per-protocol with observed data, and repeated measures analyses).

- Changes to data calculations:
  - For Subject 23-056 (vehicle treatment group), Visit 2 data were not available. In the initial calculations, the Visit 1 data was used for Visit 2. Upon further consideration, it was decided that the data for this subject at Visit 2 (including designated study eye) would be treated as missing rather than to use the Visit 1 data as if it were recorded both at Visits 1 and 2. This decreased the number of subjects by 1 in displays requiring a study eye or change from baseline by 1 subject.

### 5.3.3 OPUS-2 Study (1118-DRY-300; SPD606-302)

#### **A Phase 3, Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Efficacy of a 5% Concentration of Lifitegrast Ophthalmic Solution Compared to Vehicle in Subjects with Dry Eye Currently Using Artificial Tears**

##### **Study Centers**

This study was performed at five investigational centers within the U. S.

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
50	43	Marc Abrams, MD	Abrams Eye Center 2322 East 22 <sup>nd</sup> St., Suite 102 Cleveland, OH 44115
51	10	Jason Bacharach, MD	North Bay Eye Associates, Inc. 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954
52	12	David Brown, III, MD	Eye Centers of Florida 4101 Evans Ave. Fort Myers, FL 33901
53	35	Joseph Gira, MD	Ophthalmology Consultants, Ltd. 12990 Manchester Rd., Suite 201 St. Louis, MO 63131

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Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
54	23	Kathleen Kelley, OD	Price Vision Group 9002 N. Meridian St., Suites. 100& 212 Indianapolis, IN 46260
55	10	Steve Lane, MD	Associated Eye Care 2950 Curve Crest Blvd. W Stillwater, MN 55082
56	30	Robert Latkany, MD	Physician Eye Care of NY 150 E 32 <sup>ND</sup> St, Suite 102 New York, NY 10016
57	34	Jodi Luchs, MD	South Shore Eye Center 2185 Wantagh Ave Wantagh, NY 11793
58	47	Joseph Martel, MD	Martel Eye Medical Group 11216 Trinity River Dr. Rancho Cordova, CA 95670
59	15	Matthew Paul, MD	Danbury Eye Physicians & Surgeons 69 Sand Pit Rd., Suite 101 Danbury, CT 06810
60	17	Muhtaba Qazi, MD	Pepose Vision Institute 1815 Clarkson Rd. Chesterfield, MO 63017
61	21	Robert Rice, MD	R and R Eye Research, LLC 5430 Fredericksberg Rd., Ste 100 San Antonio, TX 78229
62	17	Jay Rubin, MD	Eye Clinics of South Texas 999 E. Basse Rd., Suite 128-B San Antonio, TX 78209
63	37	Kenneth Sall, MD	Sall Research Medical Center 11423 187 <sup>th</sup> St., Suite 200 Artesia, CA 90701
64	9	John Sheppard, MD	Virginia Eye Consultants 241 Corporate Blvd Norfolk, VA 23502

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Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
65	49	Robert Smyth-Medina, MD	North Valley Eye Medical Group 11550 Indian Hills Rd., Suite 341 Mission Hills, CA 91345
66	26	Melissa Toyos, MD	Discover Vision Centers 4741 S. Cochise Drive Independence, MO 64055
67	17	Da-Thuy Van, MD	Houston Eye Associates 1100 Gulf Freeway, Suite 114 League City, TX 77573
68	37	Jeffery Whitsett, MD	Whitsett Vision Group 1237 Campbell Rd Houston, TX 77055
70	56	Dave Wirta, MD	Eye Research Foundation 520 Superior Ave., Suite 235 Newport Beach, CA 92663
71	0	Brad Feldman, MD	Philadelphia Eye Associates 1703 S Broad St., Suite 103 Philadelphia, PA 19148
72	14	Michael Korenfeld, MD	Comprehensive Eye Care, Ltd. Vision Research Institute 901 East 3 <sup>rd</sup> St. Washington, MO 63090
73	24	Stefan Trocme, MD	Intouch Clinical Research Center 11550 Fuqua #250 Houston, TX 77034
74	8	Gary Wortz, MD	Kentucky Center for Vision D.B.A. Koffler Vision Group 120 N. Eagle Creek Dr., Suite 431 Lexington, KY 40509
75	7	Parag Majmudar, MD	Chicago Cornea Consultants, Ltd. 1585 N. Barrington Rd., Suite 502 Hoffman Estates, IL 60169
76	5	Robert Sorenson, MD	Inland Eye Specialists 3953 W. Stetson Ave. Hemet, CA 92545

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
77	32	Reginald Sampson, MD	Montebello Medical Center, Inc. 229 E. Beverly Blvd. Montebello, CA 90640
78	33	Michael Gadsby, MD	Hull Eye Center 1739 West Avenue J Lancaster, CA 93534
79	9	Kathryn Richdale, MD, PhD	SUNY College of Optometry Clinical Vision Research Center 33 West 42 <sup>nd</sup> Street New York, NY 10036
80	14	Joseph Tauber, MD	Tauber Eye Center 4400 Broadway Suite 202 Kansas City, MO 64111

**Source:** Module 5.3.5.1.1\ 1118-DRY-300\ Section 16.1.4

## Study Objectives

### Primary:

- To evaluate the efficacy of lifitegrast ophthalmic solution (5%) compared to vehicle in the treatment of dry eye in subjects currently using artificial tears as assessed by the co-primary endpoints of:
  - Sign – inferior corneal fluorescein staining score (0-4 point scale) measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye
  - Symptom – eye dryness score (0-100 point visual analogue scale, both eyes) measured by mean change from baseline to Day 84 (Week 12, Visit 5)
- To evaluate the safety and tolerability of lifitegrast compared to vehicle in subjects with dry eye when administered twice daily for 84 days (12 weeks).

### Secondary:

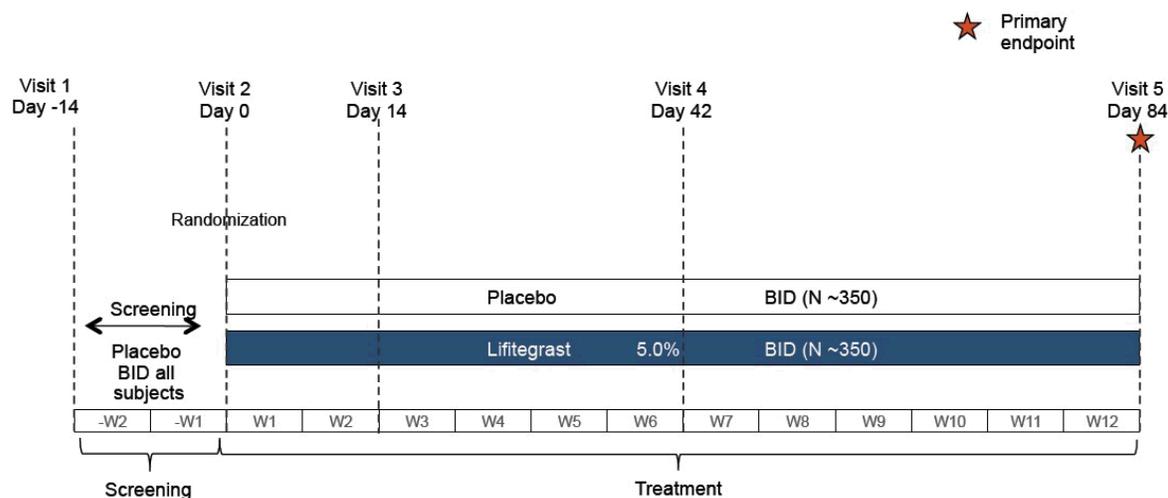
To evaluate the efficacy of lifitegrast compared to vehicle in the treatment of dry eye in subjects currently using artificial tears as assessed by:

- Sign: total corneal staining score (0-12 point scale), measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated eye
- Sign: nasal conjunctival lissamine green staining score (0-4 point scale), measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye
- Symptom: eye discomfort score (0-100 point VAS, both eyes), measured by mean change from baseline to Day 84 (Week 12, Visit 5)
- Symptom: Ocular Dryness Score (ODS) (0-4 point scale), measured by mean change from baseline to Day 84 (Week 12, Visit 5) in the designated study eye.

**Methodology:**

This was a Phase 3, multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel-arm study conducted in the US stratified by inferior corneal staining score ( $\leq 1.5$  or  $> 1.5$ ) and eye dryness score ( $< 60$  or  $\geq 60$ ). Approximately 700 subjects with dry eye disease were randomized to lifitegrast or vehicle at Visit 2 (Day 0, Week 0) and were instructed to follow a twice daily dosing regimen for 12 weeks. Subjects were required to use artificial tears within 30 days of Visit 1 (Day -14, Week -2), but artificial tear use was not permitted during the study.

**Figure 5.3.3-1 Study Design Schematic**



**Screening Period**

The Screening Period included 2 visits (Visits 1 and 2). Each visit included exposure to the controlled adverse environment (CAE). Subjects had to have an inferior corneal staining score of  $\geq 0.5$  (0-4 point scale with allowance for 0.5 point increments) in at least 1 eye with a Schirmer’s Tear Test (STT) score  $\geq 1$  and  $\leq 10$  mm in the same eye at Visit 1 (Day -14, Week -2) and had to replicate these findings in the same eye at Visit 2 (Day 0, Week 0) in order to be eligible for the study. The worst eye (highest score) meeting these requirements was designated as the study eye.

**Treatment Period**

The treatment period started at Visit 2 (Day 0, Week 0) and included Visits 3-5 (Days 14-84, Weeks 2-12). Site staff administered the first dose of randomized investigational product at Visit 2 (Day 0, Week 0) and administered a dose at each subsequent scheduled visit. Subjects self-administered investigational product for all other doses until Visit 5 (Day 84, Week 12).

**Study Population**

**Inclusion Criteria**

Individuals eligible to participate in this study were to have met all of the following criteria:

1. Willing and able to read, sign, and date the informed consent and Health Insurance Portability and Accountability Act documents after the nature of the study had been explained and prior to initiation of Visit 1 procedures or exams
2. Willing and able to comply with all study procedures
3. Was at least 18 years of age at the time of enrollment
4. Male or female
5. As needed or scheduled use of non-prescription (OTC) artificial tear substitute for symptoms of dry eye within past 30 days prior to Visit 1 (Day -14, Week -2) and willing to suspend use of tear substitutes 72 hours prior to Visit 1 (Day -14, Week -2) until completion of the study
6. Best corrected visual acuity of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye at Visit 1 (Day -14, Week -2)
7. Subject-reported history of dry eye in both eyes
8. Corneal fluorescein staining score  $\geq 2$  (0-4 point scale) in at least 1 region in at least 1 eye at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0)
9. Conjunctival redness score  $\geq 1$  (0-4 point scale with allowance for 0.5 point increments) in at least 1 eye at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0)
10. Eye dryness score  $\geq 40$  (0-100 point VAS, both eyes) at Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0)
11. A positive response in at least 1 eye, defined as meeting ALL of the following criteria in the same eye at both Visits 1 and 2 (Days -14 and 0, Weeks -2 and 0):
  - a) Inferior corneal fluorescein staining score  $\geq 0.5$  (0-4 point scale with allowance for 0.5 increments)
  - b) Schirmer Tear Test (without anesthesia)  $\geq 1$  and  $\leq 10$  mm
12. A negative urine pregnancy test if female of childbearing potential (those who were not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or post-menopausal [12 months after last menses]) and must have used adequate birth control throughout the study period. Adequate birth control was defined as hormonal-oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner.
13. Subjects with secondary Sjogren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosus) or other autoimmune diseases (e.g., multiple sclerosis, inflammatory bowel disease) were eligible for enrollment consideration provided the subject met all other inclusion and exclusion criteria, AND were not in a medical state – in the opinion of the principal investigator – that could have interfered with study parameters, were not taking systemic/ocular steroids, and were not immunodeficient/immunosuppressed (e.g., receiving systemic immunomodulating or immunosuppressive drugs to manage their baseline medical state).

**Reviewer's Comment:**

*In Study 118-KCS-200 (OPUS-1), subjects who had used or desired to use artificial tears for symptoms of dry eye within past 6 months, without any affirmation that artificial tears had actually been used, were eligible for the study. By contrast, in Study 1118-DRY-300 (OPUS-2), subjects who had actually used artificial tears within 30 days prior to Visit 1, were eligible for enrollment in the study.*

*Minimal sign and symptom scores were required for study entry.*

### **Exclusion Criteria**

Individuals who met any of the following exclusion criteria were not to be eligible to participate in the study:

1. Contraindications to the use of the investigational product(s)
2. Known hypersensitivity to investigational product or its components
3. Received treatment with any concentration of lifitegrast, not including lifitegrast vehicle (vehicle), in a previous clinical study
4. Any ocular condition that, in the opinion of the investigator, could have affected study parameters including, but not limited to, lid margin disorders (e.g., blepharitis including staphylococcal, demodex, or seborrheic; meibomian gland disease, excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, and/or active ocular inflammation.
5. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
6. Active or history of ocular herpes; any other ocular infection within the last 30 days
7. Unwilling to avoid wearing contact lenses for 7 days prior to and for duration of the study period
8. Positive urine pregnancy test or nursing an infant
9. Any blood donation or significant loss of blood within 56 days of Visit 1
10. Any history of immunodeficiency disorder, human immunodeficiency virus, positive hepatitis B, C, or evidence of acute active hepatitis A (anti-hepatitis A virus immunoglobulin M), or organ or bone marrow transplant
11. Use prohibited medications (topical, topical ophthalmic, systemic, and/or injectable) during the appropriate pre-study washout period (see below) and during the study. Prohibited medications included topical cyclosporine or use of any other ophthalmic medication (e.g., glaucoma medication, topical anti-inflammatory eye drops) for the duration of the study. The appropriate pre-study washout period was as follows:
  - a) Antihistamines (including ocular): 72 hours prior to Visit 1
  - b) Oral aspirin or aspirin-containing products allowed if dose was stable over past 30 days prior to Visit 1 and no change in dose anticipated during the study
  - c) Topical cyclosporine: 6 weeks prior to Visit 1
  - d) Corticosteroids or mast cell stabilizers (including ocular): 14 days prior to Visit 1
  - e) Any medication (oral or topical) known to cause ocular drying that had not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study; antihistamines were not allowed at any time during the study
  - f) All other topical ophthalmic preparations (including artificial tear substitutes other than the study drops: 72 hours prior to Visit 1
12. Any significant chronic illness that, in the opinion of the investigator, could have interfered with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes

13. Use of any investigational product or device within 30 days prior to Visit 1 or during the study period
14. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any scheduled ocular surgical procedure during the study period
15. History of yttrium aluminum garnet laser posterior capsulotomy in past 6 months prior to Visit 1
16. Known history of alcohol and/or drug abuse within the past 12 months, that in the opinion of the principal investigator, may have interfered with study compliance, outcome measures including safety parameters, and/or the general medical condition of the subject
17. Subjects with dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or destruction of conjunctival goblet cells (as with vitamin A deficiency) were not eligible for the study. Subjects with incidental scars secondary to refractory surgery (i.e., LASIK surgery) that, in the opinion of the principal investigator, would not interfere with study compliance and/or outcome measures were not excluded from the study.

#### **Removal of Subjects**

Same as described in OPUS-1.

#### **Administration of Investigational and Reference Products**

Same as described in OPUS-1.

#### **Identity of Investigational and Reference Products**

Lifitegrast was supplied as a sterile, clear, colorless liquid solution containing 5% lifitegrast in 5 (b) (4) single dose, low-density polyethylene unit dose (b) (4) with a fill volume of approximately (b) (4). Each mL of a 5% solution contained 50 mg of lifitegrast. In addition to lifitegrast, the solution contained (b) (4). (b) (4). The batch number for lifitegrast was 2F11.

The reference product was visually indistinguishable from the active solution. It consisted of all components of the lifitegrast solution with the exception of the active drug. The batch numbers for the vehicle were 2E57 and 2E60.

#### **Method of Assigning Subjects to Treatment Groups**

Subjects were randomly assigned to receive lifitegrast or vehicle based on a 1:1 ratio in the within the randomization strata using permuted blocks.

Randomization was centralized across study centers, stratified by Visit 2 inferior fluorescein corneal staining score and eye dryness score in the study eye in order to balance amongst the treatment groups. An interactive web response system (IWRS) was used to facilitate subject randomization, accounting for the stratification factors. Subjects were classified into 1 of the following strata based on site calculation and entry in the IWRS:

- Visit 2 (Day 0, Week 0) inferior corneal staining score  $\leq 1.5$  in the study eye and eye dryness score  $< 60$

- Visit 2 (Day 0, Week 0) inferior corneal staining score  $\leq 1.5$  in the study eye and eye dryness score  $\geq 60$
- Visit 2 (Day 0, Week 0) inferior corneal staining score  $> 1.5$  in the study eye and eye dryness score  $< 60$
- Visit 2 (Day 0, Week 0) inferior corneal staining score  $> 1.5$  in the study eye and eye dryness score  $\geq 60$

### **Prohibited and Concomitant Treatment**

All prescription and over-the-counter medications taken by a subject for 60 days prior to Day -14 (Week -2, Visit 1) through the end of the study (Day 84 [Week 12, Visit 5]) were recorded on the eCRF. The investigator may have prescribed additional medications during the study, as long as the prescribed medication was not prohibited by the protocol. In the event of an emergency, any needed medications were prescribed without prior approval, but the medical monitor must have been notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study were recorded on the eCRF.

### **Criteria for Evaluation**

The following efficacy assessments were performed at every study visit:

#### Ocular Signs

- Corneal fluorescein staining score (superior, central, and inferior regions and total score [derived as sum of all 3 regions])
- Conjunctival lissamine green staining score (temporal and nasal regions and total score [derived as sum of both regions])
- Conjunctival redness score
- Schirmer Tear Test (without anesthesia)

#### Ocular Symptoms

- Visual analogue scale (individual items of burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, and pain)
- Ocular discomfort score
- Ocular Surface Disease Index (visual-related function, environmental triggers, and symptoms subscales).

The following safety measurements were collected at every study visit (except where noted otherwise):

- Adverse events (ocular and non-ocular)
- Best corrected visual acuity
- Slit lamp biomicroscopy
- Dilated funduscopy (Visits 1 and 5)
- Drop comfort (Visits 2-5)

### **Statistical Methods**

#### **Determination of Sample Size**

For the primary ocular sign, a 0.25 unit difference between lifitegrast and vehicle in the mean change from baseline to Day 84 (Visit 5) in inferior corneal staining, with a common SD of 0.95

units was assumed. Under these assumptions, a sample size of 350 subjects per treatment group would yield approximately 93% power to show a significant difference at the  $\alpha=0.05$  level under a 2-sample t-test.

For the primary ocular symptom, a 10.0 unit difference between lifitegrast and vehicle in the mean eye dryness score at Day 84 (Visit 5) with a common SD of 40 units was assumed. Under these assumptions, a sample size of 350 subjects per treatment group would yield approximately 91% power to show a significant difference at the  $\alpha=0.05$  level under a 2-sample t-test.

It was expected that no subjects would be excluded from the primary analysis due to missing data given the proposed primary analysis method.

### **Evaluability**

#### **Randomized Population:**

Included all randomized subjects

#### **Safety Population:**

All randomized subjects who received at least 1 dose of investigational product.

#### **Intent-to-Treat Population:**

All randomized subjects who received at least 1 dose of investigational product (Primary efficacy analysis population).

The ITT and Safety Populations were identical for this study. Analyses conducted using the ITT Population were based upon treatment assigned, while analyses conducted using the Safety Population were based upon the treatment received.

### **Handling of Dropouts or Missing Data**

For the efficacy data, subjects were analyzed either based upon observed data or LOCF. Other data collected, including missing dates, were, in general, not imputed and were displayed as observed. For analyses based on LOCF, data were taken from the last date collected without regard to analysis window flag. For imputation of derived variables for LOCF, missing derived variables at a visit were carried forward rather than carrying forward individual items and then calculating the derived variable. This ensured that all components for a derived variable reflected data collected at the same visit. For AEs and concomitant medications, partial dates were used to classify events as before or after treatment. Where the partial dates did not allow such a classification, the event was assumed to be after treatment.

### **Efficacy Analyses**

#### **Primary Efficacy Analyses**

The primary analysis of the following co-primary endpoints was performed using a stratified 2-sample t-test comparing lifitegrast to vehicle in the ITT Population with LOCF. The ANOVA model included treatment, strata, and the interaction between treatment and strata:

- Ocular Sign: Mean change from baseline to Day 84 (Visit 5) in inferior corneal fluorescein staining score (0-4 Ora scale)

- Ocular Symptom: Mean change from baseline to Day 84 (Visit 5) in eye dryness score (0-100 visual analogue scale, both eyes).

### **Secondary Efficacy Analyses**

The following secondary efficacy endpoints were analyzed similarly to the co-primary efficacy endpoints:

- Ocular signs: Mean change from baseline to Day 84 in total corneal fluorescein staining score and nasal conjunctival lissamine green staining score in the designated study eye
- Ocular symptoms: Mean change from baseline to Day 84 in eye discomfort score and ODS in the designated study eye.

The endpoints were analyzed using the same ANOVA model as for the coprimary efficacy endpoints comparing lifitegrast to vehicle in the ITT Population with LOCF. Hochberg's procedure was applied to control the type I error rate at 5% level across all secondary endpoints. In applying Hochberg's procedure, nominal p-values were produced and the adjustment applied at the time the p-values were interpreted for statistical significance.

To apply Hochberg's procedure of multiple testing, the higher p-value was compared with 5% level. If this p-value was <5%, then both the secondary sign endpoints were declared significant. If the higher p-value was not <5%, then the smaller p-value was compared with 2.5%. If the smaller p-value was < 2.5%, then the secondary sign endpoint corresponding to this smaller p-value was declared significant. The same was applied to the 2 symptom endpoints.

### **Sensitivity Analyses for the Coprimary and Secondary Endpoints**

The coprimary efficacy endpoints and secondary endpoints were analyzed using additional statistical methods as sensitivity analyses. The planned sensitivity analyses consisted of repeating the primary analysis using observed data, a stratified rank-based test (i.e., Wilcoxon) with LOCF, and repeated measures ANOVA (no imputation). The stratified rank-based test consisted of repeating the primary analysis (LOCF) using the overall ranks rather than the observed data. The repeated measures analysis modeled the outcome as a function of the randomization strata, treatment, and time. In this model, all the model terms were treated as categorical variates with a common treatment effect assumed over time and the randomization strata (i.e., main effects model). An unstructured covariance matrix was used for this analysis.

Subjects assigned to the incorrect strata during randomization were analyzed using the stratification used for the randomization. The coprimary efficacy endpoints were analyzed using the strata that would have been the correct strata based on the baseline characteristics of the subjects.

### **Safety Analyses**

All safety analyses were performed on the Safety Population. Descriptive analyses of the following safety variables were summarized by treatment group:

- Frequency and severity of TEAEs (overall, ocular, and non-ocular)
- BCVA

- Slit lamp biomicroscopy
- Drop comfort assessment upon instillation, and 1, 2, and 3 minutes post-instillation (Visits 2 – 5)
- Dilated fundoscopy (Visits 1 and 5).

### **Changes in Study Conduct**

The original protocol (Version 1.0, dated 06 Nov 2012) was amended once on 06 Sep 2013.

In addition to minor editorial changes, the major changes included the following:

- The study objectives and efficacy outcome measures were updated to clarify that they would be measured in the designated study eye, where appropriate, and be measured as the mean change from baseline rather than the Day 84 (Week 12, Visit 5) score.
- The corneal and conjunctival staining regions to be scored were specified.
- The OSDI trigger subscale was renamed the environmental trigger subscale.
- The t-test analysis to compare average drop comfort scores was removed.
- The Randomized Population was added.
- The ANOVA model for the primary efficacy analysis was specified. References were cited and added for the stratified, 2-sample t-test.

### **Changes in the Planned Analyses**

No changes were made to the planned analyses. Additional graphical presentations of the data were prepared than stated in the SAP.

Figure 2 – Study Assessments

Procedure	Visit 1 Day -14 ± 3	Days -13 to -1	Visit 2 Day 0			Days 1–13	Visit 3 Day 14 ± 3	Days 15–41	Visit 4 Day 42 ± 4	Days 43–83	Visit 5 Day 84 ± 8	ET/ UNS
			Pre- random- ization	Random -ization	Post- random- ization							
Informed consent	X											
Demographic data	X											
Height and weight (subject-reported)	X											
Medical history/medication history	X											
Concomitant medication review			X				X		X		X	X
Inclusion/exclusion criteria	X		X									
Urine pregnancy test	X		X				X		X		X	X
<b>Subjective Measures</b>												
VAS	X		X				X		X		X	X
ODS	X		X				X		X		X	X
OSDI	X		X				X		X		X	X
Drop comfort					X		X		X		X	
<b>Objective Measures</b>												
BCVA	X		X				X		X		2X	X
Slit lamp biomicroscopy	X		X				X		X		2X	X
Conjunctival redness score	X		X				X		X		X	X
Corneal staining (fluorescein)	X		X				X		X		X	X
Conjunctival staining (lissamine)	X		X				X		X		X	X

Procedure	Visit 1 Day -14 ± 3	Days -13 to -1	Visit 2 Day 0			Days 1-13	Visit 3 Day 14 ± 3	Days 15-41	Visit 4 Day 42 ± 4	Days 43-83	Visit 5 Day 84 ± 8	ET/ UNS
			Pre- random- ization	Random- ization	Post- random- ization							
STT (without anesthesia)	X		X				X		X		X	X
Dilated funduscopy	X										X	X
<b>Investigational Product Treatment</b>												
Open-label placebo administration at study site	X		X									
Open-label placebo dispensation	X											
Open-label placebo administration at home		X										
Placebo vial collection			X									X
Randomization				X								
Investigational product administration at study site					X		X		X		X	
Investigational product dispensation					X		X		X			
Investigational product administration at home					X	X	X	X	X			
Investigational product collection						X		X			X	X
AE assessment	X	X	X		X	X	X	X	X	X	X	X
Study exit											X	X

AE=adverse event; BCVA=best corrected visual acuity; ET=Early Termination Visit; ODS=ocular discomfort score; OSDI=Ocular Surface Disease Index; STT=Schirmer Tear Test; UNS=unscheduled visit; VAS=visual analogue scale

### 5.3.4 SONATA Study (1118-DRY-400; SPD606-303)

#### **A Phase 3, Multicenter, Randomized, Double-masked and Placebo-controlled Study Evaluating the Safety of a 5% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye**

##### **Study Centers**

This study was performed at twenty-two investigational centers within the U. S.

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
31	20	Marc Abrams, MD	Abrams Eye Center 2322 East 22 <sup>nd</sup> St., Suite 102 Cleveland, OH 44115
32	18	Doug Day, MD	Coastal Research Associates, LLC 11215 Alpharetta Highway, Suite J3 Roswell, GA 30076
33	3	Eric Donnenfeld, MD	Ophthalmic Consultants of Long Island 200 North Village Ave., Suite 402 Rockville Centre, NY 11570
34	21	Alan Gruber, MD	Rochester Ophthalmological Group, PC 2100 South Clinton Ave. Rochester, NY 14618
35	9	William Hammonds, MD	Southeast Clinical Research Associates 6035 Fairview Rd. Charlotte, NC 28210
36	6	Edward Holland, MD	Cincinnati Eye Institute 580 South Loop Rd., Suite 200 Edgewood, KY 41017
37	7	John Hovanesian, MD	Harvard Eye Associates 24401 Calle de la Louisa, Suites 300-312 Laguna Hills, CA 92653
38	11	Charles Kirby, MD	Chattanooga Eye 5715 Cornelison Rd., #6600 Chattanooga, TN 37411

Clinical Review  
Rhea A. Lloyd, MD  
NDA 208-073  
Lifitegrast ophthalmic solution, 5%

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
39	16	Steve Lane, MD	Associated Eye Care 2950 Curve Crest Blvd. W Stillwater, MN 55082
40	25	Parag Majmudar, MD	Chicago Cornea Consultants, Ltd. 1585 N. Barrington Rd., Suite 502 Hoffman Estates, IL 60169
41	30	Kelly Nichols, OD	University of Houston 505 J. Davis Armistead Building Houston, TX 77204
42	31	Kenneth Sall, MD	Sall Research Medical Center 11423 187 <sup>th</sup> St., Suite 200 Artesia, CA 90701
43	13	Barry Schechter, MD	Florida Eye Microsurgical Inst., Inc. 1717 Woolbright Rd. Boynton Beach, FL 33426
44	19	Elizabeth Sharpe, MD	Glaucoma Consultants & Center for Eye Research 721 Longpoint Rd., Suite 407 Mt. Pleasant, SC 29464
45	28	Michael Tepedino, MD	Cornerstone Eye Care 1400 East Harley Drive High Point, NC 27261
46	24	Gary Wortz, MD	Kentucky Center for Vision D.B.A. Koffler Vision Group 120 N. Eagle Creek Dr., Suite 431 Lexington, KY 40509
47	16	Jai Parekh, MD	Brar-Parekh Eye Associates 1031 McBride Ave., Suite D106 Woodland Park, NJ 07424
48	7	Robert Sorenson, MD	Inland Eye Specialists 3953 W. Stetson Ave. Hemet, CA 92545
49	8	Cynthia Matossian, MD	Matossian Eye Associates 2 Capital Way, Suite 326 Pennington, NJ 08534

Clinical Review  
Rhea A. Lloyd, MD  
NDA 208-073  
Lifitegrast ophthalmic solution, 5%

Site No.	No. of Randomized Subjects	Principal Investigator	Site Name and Address
90	7	Michael Gadsby, MD	Hull Eye Center 1739 West Ave., J Lancaster, CA 93534
91	2	C. Starck Johnson, MD	Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134
92	11	Reginald Sampson, MD	Montebello Medical Center, Inc. 229 E. Beverly Blvd. Montebello, CA 90640

Source: Module 5.3.5.1\1118-DRY-400\ Section 16.1.4

### Study Objectives

#### Primary:

To evaluate the safety of lifitegrast ophthalmic solution 5% compared to vehicle in the treatment of dry eye as assessed by ocular and non-ocular adverse events (AEs) when administered twice daily for 360 days (approximately 1 year).

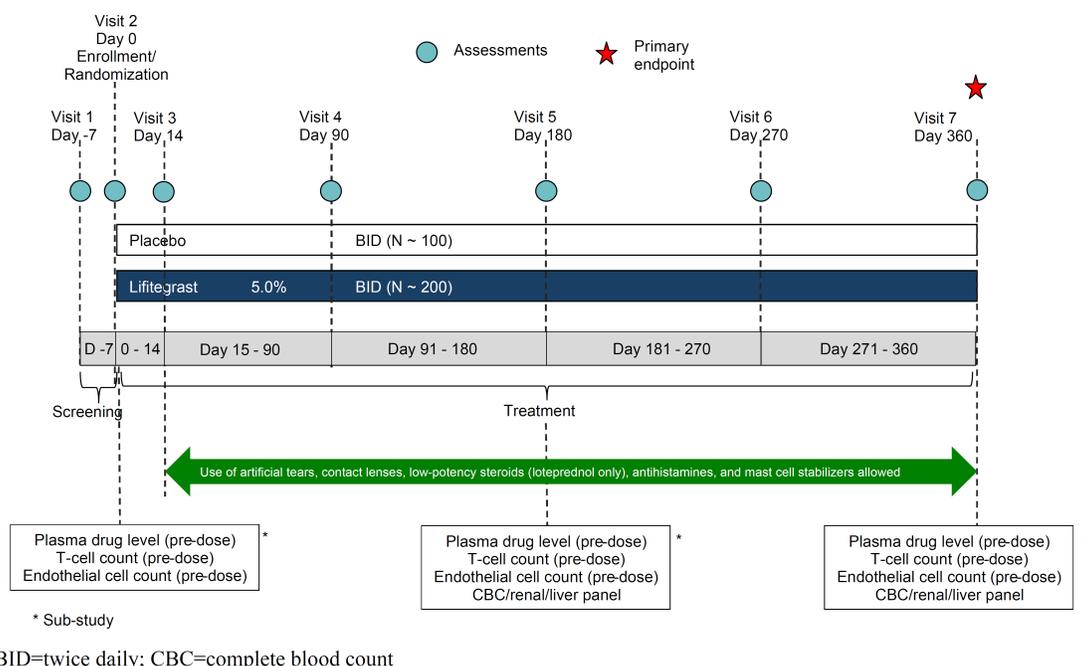
#### Secondary:

To evaluate the ocular safety measures of lifitegrast ophthalmic solution 5% compared to vehicle in subjects with dry eye when administered twice daily for 360 days (approximately 1 year).

### Methodology

This was a Phase 3, multicenter, randomized, prospective, double-masked, vehicle-controlled, parallel arm study conducted in the US. Three hundred and thirty-two subjects with dry eye disease were randomized 2:1 to received either lifitegrast ophthalmic solution 5% or vehicle solution as topical ophthalmic drops administered bilaterally twice daily for 360 days (approximately 1 year).

## Study Design Schematic



Source: CSR Module 5.3.5.1\1118-DRY-400\Section 3.2

## Study Population

### Inclusion Criteria

Individuals eligible to participate in this study must have met all of the following criteria:

1. Willing and able to read, sign, and date the informed consent and HIPAA documents after the nature of the study was explained and prior to initiation of Visit 1 (Day -7, Week -1) procedures or exams
2. Willing and able to comply with all study procedures
3. Was at least 18 years of age at the time of enrollment
4. Male or female
5. Use and/or desire to use artificial tear substitute for symptoms of dry eye within past 6 months.
6. Best corrected visual acuity of 0.7 logMAR or better (Snellen equivalent score of 20/100 or better) in each eye using a refraction within 6 months prior to visit 1 (Day -7, Week -1)
7. Subject-reported history of dry eye in both eyes
8. Corneal fluorescein staining score  $\geq 2.0$  (0-4 point scale) in at least 1 region in either eye at both Visits 1 and 2 (Days -7 and 0, Week -1 and 0)
9. Visual analogue scale score  $\geq 40$  in either symptom of eye dryness or discomfort at Visit 1 (Day -7, Week -1)
10. Schirmer Tear Test (without anesthesia)  $\geq 1$  and  $\leq 10$  mm in either eye at Visit 1 (Day -7, Week -1)
11. A negative urine pregnancy test if female of childbearing potential (those who were not surgically sterilized [bilateral tubal ligation, hysterectomy, or bilateral oophorectomy] or

post-menopausal [12 months after last menses]) and must have used adequate birth control throughout the study period. Adequate birth control was defined as hormonal-oral, implantable, injectable, or transdermal contraceptives; mechanical – spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device; or surgical sterilization of partner.

12. Subjects with secondary Sjogren’s syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosus) or other autoimmune diseases (e.g., multiple sclerosis, inflammatory bowel disease) were eligible for enrollment consideration provided the subject met all other inclusion and exclusion criteria, AND, were not in a medical state – in the opinion of the principal investigator – that could have interfered with study parameters, were not taking systemic steroids, and were not immunodeficient/ immunosuppressed (e.g., receiving systemic immunosuppressive/ immunomodulatory drugs to manage their baseline medical state)
13. Subjects who electively used contact lenses may have participated in the study provided they:
  - a. Had corrective eyeglasses (required for ALL visits including Visit 1 [Day -7, Week -1]); refraction should have been no older than 6 months prior to Visit 1 [Day -7, Week -1)
  - b. Were not required to use contact lenses for medical reasons (e.g., Boston Ocular Surface Prosthesis)
  - c. Could refrain from contact lens use from Visit 1 [Day -7, Week -1] until after Visit 3 ( Day 14, Week 2) assessments were complete, and not within 15 minutes after investigational product administration throughout the remainder of the study
  - d. Had the contact lenses fitted > 90 days prior to enrollment
  - e. Had no ongoing medical problems with the comfort or fit of the contact lenses
  - f. Did not anticipate any change in contact lenses or corrective eyeglasses in the next 12 months
  - g. Used only daily disposable lenses for this study

### **Exclusion Criteria**

Individuals who met any of the following exclusion criteria were not eligible to participate in the study:

1. Contraindications to the use of the investigational product(s)
2. Known hypersensitivity to investigational product or its components
3. Received treatment with any concentration of lifitegrast ophthalmic solution, not including lifitegrast vehicle in a previous clinical trial
4. Any ocular condition that, in the opinion of the investigator, could have affected study parameters including, but not limited to, glaucoma, diabetic retinopathy, blepharitis, meibomian gland disease, follicular conjunctivitis, iritis, uveitis, wet-exudative age-related macular degeneration, retinal vein occlusion, and/or active ocular inflammation
5. Use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
6. Active or history of ocular herpes; any other ocular infection within the last 30 days
7. Positive urine pregnancy test or nursing an infant
8. Any blood donation or significant loss of blood within 56 days of Visit 1 (Day -7, Week -

- 1)
9. Any history of immunodeficiency disorder, human immunodeficiency virus, positive hepatitis B, C, or evidence of acute active hepatitis A (antihepatitis A virus immunoglobulin M), or organ or bone marrow transplant
10. Use of the following prohibited medications during the appropriate pre-study washout period and at any time during the study:
  - a. 14 days prior to Visit 1
    - i. Topical ophthalmic non-steroidal anti-inflammatory agents
  - b. 6 weeks prior to Visit 1:
    - i. Topical ophthalmic cyclosporine
    - ii. Systemic steroids (IV, IM, IA, oral)
11. Use of the following medications/ procedures were allowed after Visit 3 (Day 14, Week 2); however, were prohibited during the appropriate pre-study washout period through the completion of Visit 3 (Day 14, Week 2), and any allowed topical ophthalmic treatment must have been administered or contact lenses inserted > 15 minutes after administration of investigational product:
  - a. 24 hours prior to Visit 1
    - i. Use of contact lenses and/or contact lens wetting solutions
  - b. 72 hours prior to Visit 1
    - i. Topical ophthalmic/nasal antihistamines
    - ii. Artificial tears
  - c. 14 days prior to Visit 1
    - i. Topical ophthalmic/ nasal steroids; only loteprednol was allowed after Visit 3 (Day 14, Week 2) for up to 4 weeks at a time
    - ii. Topical ophthalmic/nasal mast cell stabilizers
12. Any significant chronic illness or abnormal screening clinical laboratory parameter that, in the opinion of the investigator, could have interfered with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, poorly controlled diabetes, and/ or clinically significant hematologic, renal or liver disease.
13. Use of any investigational product or device within 30 days prior to Visit 1 (Day -7, Week 1) or during the study period
14. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1 (Day -7, Week 1) and/or any other ocular surgical procedure within 12 months prior to Visit 1 (Day -7, Week 1); or any scheduled ocular surgical procedure to be conducted during the study period
15. History of YAG laser capsulotomy within 6 months prior to Visit 1
16. Known history or alcohol and/ or drug abuse within the past 12 months, that in the opinion of the principal investigator, may have interfered with study compliance outcome measures including safety parameters, and/or the general medical condition of the subject
17. Subjects with dry eye secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatricial pemphigoid) or destruction of conjunctival goblet cells (as with vitamin A deficiency) were not eligible for the study. Subjects with incidental scars secondary to refractory surgery (i.e., LASIK surgery) that in the opinion of the principal investigator would not interfere with study compliance and/or outcome measures were not excluded from the study.

## Removal of Subjects

Same as OPUS-1.

## Identity of Investigational and Reference Products

Investigational product was supplied as a sterile, clear, liquid solution containing 5% lifitegrast concentration in 5 (b) (4) single-dose, (b) (4) low-density polyethylene unit dose (b) (4) with a fill volume of approximately 0.2 mL. Each mL of a 5% solution contained 50 mg of lifitegrast. In addition to lifitegrast, the components of the solution were: (b) (4). The lifitegrast batch number was 2F11.

The vehicle consisted of all components of the investigational product solution with the exception of lifitegrast. The batch numbers were 2F57 and 2E60.

## Bioanalytical Measurements

### Sample Collection and Handling

Serial blood samples were obtained at Days 0, 180±5, and 360±5 for determination of lifitegrast concentrations in plasma in a subset of approximately 25% of subjects at selected participating sites. A total of approximately 24 mL of blood was collected per subject for the determination of lifitegrast concentrations in plasma during the study.

Once each sample was collected, it was mixed immediately by gently inverting the tube at least 8-10 times and centrifuged until cells and plasma were well separated. The plasma was extracted by pipette and frozen at -20°C until shipment to the central laboratory for analysis.

### Bioanalytical Methodology

Serial blood samples were obtained at Days 0, 180±5, and 360±5 for determination of lifitegrast concentrations in plasma in a subset of approximately 25% of subjects at selected participating sites. A total of approximately 24 mL of blood was collected per subject for the determination of lifitegrast concentrations in plasma during the study.

Once each sample was collected, it was mixed immediately by gently inverting the tube at least 8-10 times and centrifuged until cells and plasma were well separated. The plasma was extracted by pipette and frozen at -20°C until shipment to the central laboratory for analysis.

## Pharmacokinetic Measurements

The trough concentration of lifitegrast in plasma was assessed at Visit 2 (Day 0, Month 0) (baseline for lifitegrast levels), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) in approximately 25% of subjects (N=75) at selected participating sites. No formal pharmacokinetic profiling was planned.

## Analysis Populations

### Randomized Population:

All randomized subjects

### Safety Population:

All randomized subjects who received at least 1 dose of investigational product.

### **Determination of Sample Size**

The study sample size was based on guidance provided by the FDA and is consistent with the ICH guidance on exposure for drugs intended for long-term treatment of non-life threatening conditions (ICH 1995). The sample size was not based on statistical calculations or statistical assumptions.

### **Handling of Dropouts or Missing Data**

Data, including missing dates, were not imputed and were displayed as observed. For adverse events and concomitant medications, partial dates were used to classify events as before or after treatment. If the partial dates did not allow such classification, the event was assumed to be after treatment. If a complete date was not available for the date of the last randomized investigational product dose, then the last date of the on-site administration of investigational product was used for the computation of exposure and compliance to randomized investigational product.

### **Efficacy Analyses**

None performed.

### **Safety Analyses**

#### **Primary Safety Analysis**

The primary safety assessment was based upon the percentage and severity of ocular and non-ocular treatment emergent adverse events (TEAEs). Adverse events were classified by the investigator as ocular or non-ocular. Statistical analyses were descriptive in nature.

A brief summary of TEAEs, serious TEAEs, deaths, TEAEs leading to investigational product discontinuation, and TEAEs by severity was presented by treatment arm and overall for all TEAEs, ocular TEAEs, and non-ocular TEAEs. The number and percentage of subjects with ocular and non-ocular TEAEs was tabulated by system organ class, preferred term, and treatment group (MedDRA, Version 14.1). These summaries of TEAEs were also tabulated by severity and by relationship to investigational product.

Serious TEAEs were summarized separately for ocular and non-ocular TEAEs by treatment system organ class, and preferred term. These tables were repeated with TEAEs classified by relationship to investigational product. Serious TEAEs were presented in a listing. Adverse events with a fatal outcome were summarized by treatment arm and cause of death.

Treatment discontinuations due to TEAEs or due to laboratory abnormalities were summarized by treatment arm and the reason for discontinuation. These discontinuations were also presented in a listing.

#### **Secondary Safety Analysis**

Descriptive analyses of safety measures (corneal fluorescein staining, BCVA, slit lamp biomicroscopy, drop comfort, IOP, and dilated funduscopy) were presented by treatment at all measured time points.

Study Schedule

Procedure	Visit 1 (Day -7 ±3)	Visit 2 (Day 0)	Days 1-13	Visit 3 (Day 14±4)	Days 15-89	Visit 4 (Day 90±5)	Days 91- 179	Visit 5 (Day 180 ±5)	Days 181- 269	Visit 6 (Day 270±5)	Days 271- 359	Visit 7 (Day 360±5)	ET/ UNS
Informed consent/HIPAA	X												
Demographic data	X												
Height and weight	X												
Medical history/medication history <sup>a</sup>	X	X											
Concomitant medication review		X		X		X		X		X		X	X
Inclusion/exclusion criteria	X	X											
Urine pregnancy test <sup>b</sup>	X	X		X		X		X		X		X	X
Visual analogue scale	X												
Schirmer Tear Test (without anesthesia)	X												
<b>Safety endpoint measures</b>													
Adverse event assessment		X		X		X		X		X		X	X
Drop comfort		X		X		X		X		X		X	
Best corrected visual acuity	X	X		X		X		X		X		2X	X
Slit lamp biomicroscopy	X	X		X		X		X		X		2X	X
Corneal fluorescein staining	X	X		X		X		X		X		X	X
Corneal endothelial cell count <sup>c</sup>		X						X				X	X
Clinical laboratory evaluation <sup>d</sup>	X							X				X	X
Plasma lifitegrast levels <sup>e</sup>		X						X				X	X
Blood lymphocyte counts <sup>e</sup>		X						X				X	X
Intraocular pressure	X							X				X	X

Procedure	Visit 1 (Day -7 ±3)	Visit 2 (Day 0)	Days 1-13	Visit 3 (Day 14±4)	Days 15-89	Visit 4 (Day 90±5)	Days 91- 179	Visit 5 (Day 180 ±5)	Days 181- 269	Visit 6 (Day 270±5)	Days 271- 359	Visit 7 (Day 360±5)	ET/ UNS
Dilated funduscopy	X							X				X	X
<b>Study therapy</b>													
Randomization		X											
Investigational product administration at study site		X		X		X		X		X		X	
Investigational product dispensation		X		X		X		X		X			
Investigational product administration at home			X	X	X	X	X	X	X	X	X		
Investigational product collection				X		X		X		X		X	X
Artificial tear, loteprednol, antihistamine, mast cell stabilizer drops, and contact lens (daily disposable lenses only) use allowed				X	X	X	X	X	X	X	X	X	
Study exit												X	X

<sup>a</sup> Only significant non-ocular medical history during the past year; only medications taken within the past 60 days.

<sup>b</sup> Women of childbearing potential only.

<sup>c</sup> Corneal endothelial cell counts (specular microscopy) were obtained from 60% of subjects (N=180) prior to administration of investigational product at Visits 2, 5, and 7 (Days 0, 180, and 360; Months 0, 6, and 12).

<sup>d</sup> Clinical laboratory assessments (hematologic, renal and liver functions) were performed on all subjects who met eligibility criteria at the end of Visit 1 (Day -7, Week -1). At Visits 5 and 7 (Days 180 and 360, Months 6 and 12), repeat clinical laboratory assessments were performed on approximately 25% of subjects (N=75) at selected sites.

<sup>e</sup> Plasma lifitegrast drug levels and whole blood lymphocyte (CD3, CD4, CD8) counts were obtained from approximately 25% of subjects (n=75) at about 5 study sites. Plasma and whole blood samples were obtained prior to administration of investigational product at Visits 2, 5, and 7 (Days 0, 180, and 360; Months 0, 6, and 12).

ET=Early Termination Visit; HIPAA=Health Insurance Portability and Accountability Act; UNS=unscheduled visit

**Reviewer's Comment:**

*Acceptable.*

## **Changes in Study Conduct**

The original protocol (Version 1.0, dated June 11, 2012) was amended 4 times.

### Protocol Amendment 1 (dated 27 Jun 2012)

- Increased the number of subjects included in repeat clinical laboratory assessments from 15% to 25%
- Increased the number of subjects included in whole blood lymphocyte counts from 15% to 25%, and clarified that it was to be taken from whole blood, not plasma
- Increased the number of subjects included in the assessment of the lifitegrast concentration in plasma from 15% to 25%
- Clarified the Treatment Period (Days 0-360 ± 5; Months 0-12; Visits 2-7)
- Clarified in the inclusion criteria that subjects should not have anticipated any changes in their corrective eyeglasses during the 12 months on study
- Clarified which clinical laboratory tests were included in the hematologic panel
- Added that the medical monitor must be included on SAE notifications
- Changed the subject viewing distance for measuring visual acuity from 10 feet to 13 feet.

### Protocol Amendment 2 (dated 19 Jul 2012)

- Clarified that lymphocyte counts were taken from whole blood and lifitegrast drug levels were taken from plasma
- Removed “total” from the total corneal fluorescein staining score
- Changed the size of the low-density polyethylene unit dose vials from 0.5mL to 0.99mL
- Clarified that sites only needed to fax or email SAE forms to [REDACTED]<sup>(b) (4)</sup> immediately (within 24 hours); [REDACTED]<sup>(b) (4)</sup> forwarded the SAE forms to SARcode Bioscience and the medical monitor within 1 business day upon receipt
- Revised the drop comfort assessment and instructions clarified the equipment and technique used to measure visual acuity

### Protocol Amendment 3 (dated 01 Oct 2012)

- Clarified the Screening Period (Day -7±3 to Day 0; Weeks -1 to 0; Visits 1-2)
- Changed the grading scale and instructions used to assess corneal fluorescein staining
- Clarified that only daily disposable contact lenses were allowed after Visit 3 (Day 14, Week 2)
- Corrected an error in the temperature conversion from Fahrenheit to Celsius for storage conditions
- Changed the medical monitor
- Revised the drop comfort rating scale to use a published scale (Torkildsen et al. 2008).

Protocol Amendment 4 (dated 17 Oct 2013)

- Clarified and revised the requirements for the follow-up of persisting AEs to only require discussion of ongoing ocular non-serious AEs at study completion with the medical monitor
- Added the definition of TEAEs
- Updated the title and email address of the medical monitor
- Removed the description of hypothesis testing from the data analysis conventions
- Removed the t-test for the average drop comfort rating.

**Changes in the Planned Analyses**

The statistical analysis plan states that a subgroup analysis of ocular TEAEs by loteprednol use would be performed as an exploratory objective. Loteprednol was the only topical ophthalmic steroid allowed per-protocol. All other topical ophthalmic steroids used during the study were recorded as protocol deviations. For a conservative assessment of safety, the planned subgroup analysis was expanded to include all topical ophthalmic steroid use.

## 6 Review of Efficacy – Dry Eye Indication

### Efficacy Summary

#### 6.1 Phase 2

For the treatment of the signs and symptoms of dry eye disease.

##### 6.1.1 Methods

The description of the clinical trial design is contained in Section 5.3.1. Clinical study reports, clinical protocols and literature references were submitted related to the clinical trial in support of the New Drug Application.

##### 6.1.2 Demographics

**Table 6.1.2-1 Baseline Demographic Characteristics  
ITT Population**

Variables		0.1% LIF N=57	1% LIF N=57	5% LIF N=58	Vehicle N=58
Age (years)	Mean (SD)	63.14 (13.10)	63.63 (11.88)	62.26 (12.22)	60.38 (12.93)
	Minimum, maximum	26.0, 89.0	35.0, 91.0	31.0, 85.0	26.0, 89.0
	≥ 50 years, n	51	50	51	47
Sex: n (%)	Male	10 (17.5)	17 (29.8)	11 (19.0)	13 (22.4)
	Female	47 (82.5)	40 (70.2)	47 (81.0)	45 (77.6)
Race: n (%)	White	53 (93.0)	53 (93.0)	53 (91.4)	54 (93.1)
	Asian	2 (3.5)	2 (3.5)	3 (5.2)	1 (1.7)
	Black or African American	1 (1.8)	1 (1.8)	2 (3.4)	3 (5.2)
	American Indian or Alaska Native	1 (1.8)	0	0	0
	Other	0	1 (1.8)	0	0
Ethnicity: n (%)	Hispanic or Latino	1 (1.8)	0	0	0
	Not Hispanic or Latino	56 (98.2)	57 (100.0)	58 (100.0)	58 (100.0)
Iris color: n(%)	Brown	46 (40.4)	46 (40.4)	36 (31.0)	42 (36.2)
	Blue	34 (29.8)	44 (38.6)	42 (36.2)	40 (34.5)
	Hazel	24 (21.1)	18 (15.8)	30 (25.9)	20 (17.2)
	Green	10 (8.8)	4 (3.5)	6 (5.2)	12 (10.3)
	Gray	0	2 (1.8)	2 (1.7)	2 (1.7)

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Variables		0.1% LIF N=57	1% LIF N=57	5% LIF N=58	Vehicle N=58
Inferior corneal staining score (ICSS)	Mean (SD)	1.78 (0.473)	1.82 (0.508)	1.77 (0.515)	1.65 (0.513)

Source: Table 14.1.2

**Reviewer’s Comment:**

*Patient demographics were generally well-balanced across the treatment groups at baseline.*

**Prior and Concomitant Medications**

Overall, 49.6% of subjects took a prior or concomitant ocular medication. The most common (>10%) prior or concomitant medication was artificial tears. Overall, 90.9% of subjects took a prior or concomitant non-ocular medication. The most (>10%) prior or concomitant non-ocular medications were multivitamins, calcium D3, vitamin D (not otherwise-specified), fish oil, simvastatin, paracetamol, ibuprofen, acetylsalicylic acid.

**6.1.3 Subject Disposition**

A total of 545 subjects were screened, and 230 subjects were randomized after the Vehicle Run-in Period and were included in the ITT population. All of these subjects were also included in the Safety population.

The majority of subjects in all treatment groups completed the study. In the vehicle treatment group, the most common reason for discontinuation was “other” (10.3%), all of which were due to use of disallowed medication.

**Table 6.1.3-1  
 Subject Disposition  
 ITT Population**

Subject Disposition	0.1% LIF N=57 N(%)	1% LIF N=57 N(%)	5% LIF N=58 N(%)	Vehicle N=58 N(%)
Safety Population	57 (100.0)	57 (100.0)	58 (100.0)	58 (100.0)
ITT Population	57 (100.0)	57 (100.0)	58 (100.0)	58 (100.0)
Per-Protocol Population	49 (86.0)	47 (82.5)	44 (75.9)	46 (79.3)
Completed Study	54 (94.7)	51 (89.5)	48 (82.8)	48 (82.8)
Discontinued Study	3 (5.3)	6 (10.5)	10 (17.2)	10 (17.2)
<i>Reasons for Discontinuation</i>				
Adverse Event	2 (3.5)	2 (3.5)	6 (10.3)	1 (1.7)
Death	0	1 (1.8)	0	0
Lost to follow-up	0	0	1 (1.7)	2 (3.4)
Non-compliance	0	2 (3.5)	1 (1.7)	1 (1.7)

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<b>Subject Disposition</b>	<b>0.1% LIF N=57 N(%)</b>	<b>1% LIF N=57 N(%)</b>	<b>5% LIF N=58 N(%)</b>	<b>Vehicle N=58 N(%)</b>
Other	1 (1.8)	1 (1.8)	2 (3.4)	6 (10.3)

Source: CSR Table 3

**Reviewer’s Comment:**

*The subject completion rate ranged from 95% in the 0.1% lifitegrast group to 83% in the 5% lifitegrast and vehicle groups.*

*The most frequent reason for discontinuation was adverse event which was experienced by 10% of the 5% lifitegrast group, 4% of both the 0.1% and 1% lifitegrast groups and 2% of the vehicle group.*

**Table 6.1.3-2 Subjects Discontinued from Treatment or Study  
Safety Population**

<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
AE- Stinging upon instillation, lid swelling, tearing, photophobia	Lifitegrast 0.1%	001-1044	43
AE – Right hip fracture	Lifitegrast 0.1%	002-1199	78
AE – Death	Lifitegrast 1%	001-1125	52
AE – Ocular stinging/pain, tearing	Lifitegrast 1%	001-1040	7
AE – “Spider web sensation”, stinging over face	Lifitegrast 1%	005-1060	43
AE – Ocular infection	Lifitegrast 5%	001-1124	84
AE – Ocular pain	Lifitegrast 5%	001-1130	29
AE – Irritated eyes, burning upon instillation	Lifitegrast 5%	001-1159	13
AE – Stinging upon instillation	Lifitegrast 5%	002-1212	15
AE – Ocular redness, excessive tearing	Lifitegrast 5%	003-1111	43
AE – Burning upon instillation	Lifitegrast 5%	004-1138	14
AE – Conjunctivitis	Vehicle	001-1028	17
AE – Bronchitis	Vehicle	001-1136 <sup>a</sup>	15
AE – Sinus pressure, sinus infection	Vehicle	003-1110	78
AE – Bronchitis	Vehicle	004-1075	Completed
AE – Retinal vein occlusion	Vehicle	004-1142	106
Lost to follow-up	Lifitegrast 5%	001-1148	109
Lost to follow-up	Vehicle	001-1129	49
Lost to follow-up	Vehicle	004-1216	48
Noncompliance	Lifitegrast 1%	001-1223	40
Noncompliance	Lifitegrast 1%	005-1056	75

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Reason for Discontinuation	Treatment	Subject Number	Study Duration
Noncompliance	Lifitegrast 5%	001-1224	86
Noncompliance	Vehicle	004-1087	42
Other – Disallowed medication	Lifitegrast 0.1%	001-1034	38
Other – Disallowed medication	Lifitegrast 1%	004-1084	40
Other – Withdrawal of consent	Lifitegrast 5%	001-1026	11
Other – Withdrawal of consent	Lifitegrast 5%	002-1201	109
Other – Disallowed medication	Vehicle	001-1022	16
Other – Disallowed medication	Vehicle	001-1033	103
Other – Disallowed medication secondary to AE	Vehicle	001-1136 <sup>a</sup>	103
Other – Disallowed medication	Vehicle	002-1179	45
Other – Disallowed medication	Vehicle	004-1066	42
Other – Disallowed medication	Vehicle	004-1142	17

Source: Study 1118-KCS-100 CSR, Section 16.2.1

a The patient was counted twice in the CSR

**Reviewer’s Comment:**

*The number of discontinuations due to adverse events increased with increasing concentrations of lifitegrast. The most frequent reasons for discontinuation were adverse reactions related to eye irritation after instillation of lifitegrast 5%.*

**Protocol Deviations**

During a masked review of the data prior to database lock and unmasking, the sponsor reviewed the protocol deviations to determine which were considered major (i.e., had the potential to affect the efficacy or safety assessments). Subjects with major protocol deviations were excluded from the Per Protocol population.

Major protocol deviations included dosing non-compliance, non-compliance with diary assessments, intake of a prohibited medication, and missed study assessments/procedures (e.g., CAE).

#### 6.1.4 Analysis of Primary Endpoint(s)

**Table 6.1.4-1  
Primary Efficacy – Inferior Corneal Staining Score at Day 84  
ITT Population**

	0.1% LIF N=57	1% LIF N=57	5% LIF N=58	Vehicle N=58
Baseline				
n	57	56	58	58
Mean (SD)	1.78 (0.473)	1.82 (0.508)	1.77 (0.515)	1.65 (0.513)
Day 84 (Week 12, Visit5)				
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) <sup>a</sup>	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	

a Analysis of covariance model with treatment, baseline, and site. P-value compared to vehicle from Dunnett's test. Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3-uncountable, but not confluent; 4= confluent.

Note: Results presented in this table are from the study eye only.

Source: CSR, Table 6

**Reviewer's Comment:**

*The study did not meet its primary efficacy endpoint in this Phase 2 study. None of the lifitegrast groups achieved a statistically significant difference in the inferior corneal staining score at Day 83 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.*

#### 6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy results are not presented since the primary endpoint failed. Additionally, secondary endpoints were exploratory in nature, and hence no formal correction for multiplicity was to be performed.

Lifitegrast showed numerical improvements from baseline to Day 84 in the objective parameters of corneal fluorescein staining (total and inferior regions), Schirmer's tear test, and blink rate.

Lifitegrast also showed numerical improvements from baseline to Day 84 in the subjective parameters of OSDI (total, visual-related function, and trigger subscale), Ocular dryness scale, Visual analog scale (VAS) (burning/stinging, eye dryness, and itching), and 5-symptom assessment (burning, dryness, grittiness, and stinging).

#### 6.1.6 Other Endpoints

None.

#### 6.1.7 Subpopulations

Post hoc subgroup analyses of subjects with and with a history of active artificial tear use were performed. Refer to Section 6.1.10 for further details.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with finafloxacin otic suspension.

#### 6.1.10 Additional Efficacy Issues/Analyses

The applicant performed a post hoc analysis with 109 subjects who reported previous use of artificial tears (within 30 days of Visit 1) for corneal fluorescein staining.

**Table 6.1.10-1**  
**Post Hoc Analysis – Corneal Fluorescein Staining Score (Ora Scale) for Artificial Tear Users**  
**(ITT Population with LOCF)**

	0.1% LIF			1% LIF			5% LIF			Vehicle <sup>b</sup>	
	n	Mean (SD)	p-value <sup>a</sup>	n	Mean (SD)	p-value <sup>a</sup>	n	Mean (SD)	p-value <sup>a</sup>	n	Mean (SD)
<b>Total corneal region</b>											
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	<b>28</b>	<b>-0.25</b> <b>(1.42)</b>	<b>0.0280</b>	29	0.62 (1.49)
<b>Inferior corneal region</b>											
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)
<b>Change from baseline to Day 84 (Week 12, Visit 5)</b>	<b>22</b>	<b>0.25</b> <b>(0.91)</b>	<b>0.0453</b>	<b>26</b>	<b>0.15</b> <b>(0.54)</b>	<b>0.0013</b>	<b>28</b>	<b>-0.07</b> <b>(0.81)</b>	<b>0.0002</b>	<b>29</b>	<b>0.69</b> <b>(0.62)</b>
<b>Superior corneal region</b>											
Day 0 (Week 0, Visit 2, baseline)	22	1.45 (0.55)		27	1.41 (0.54)		31	1.50 (0.67)		29	1.66 (0.57)
Change from baseline to Day 14 (Week 2, Visit 3)	22	0.09 (0.78)	0.4479	26	0.06 (0.75)	0.5100	28	-0.07 (0.62)	0.9405	29	-0.09 (0.85)
Change from baseline to Day 42 (Week 6, Visit 4)	22	-0.20 (0.83)	0.7557	26	0.10 (0.92)	0.2873	28	-0.05 (0.71)	0.6520	29	-0.14 (0.69)
Change from baseline to Day 84 (Week 12, Visit 5)	22	0.16 (0.84)	0.7462	26	0.08 (0.72)	0.9630	28	-0.07 (0.78)	0.4415	29	0.09 (0.76)

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	0.1% LIF			1% LIF			5% LIF			Vehicle <sup>b</sup>	
	n	Mean (SD)	p-value <sup>a</sup>	n	Mean (SD)	p-value <sup>a</sup>	n	Mean (SD)	p-value <sup>a</sup>	n	Mean (SD)
<b>Central corneal region</b>											
Day 0 (Week 0, Visit 2, baseline)	22	0.84 (0.59)		27	1.19 (0.62)		31	0.97 (0.58)		29	1.28 (0.75)
Change from baseline to Day 14 (Week 2, Visit 3)	22	0.16 (0.68)	0.0276	26	-0.06 (0.73)	0.2536	28	-0.02 (0.60)	0.1339	29	-0.28 (0.68)
Change from baseline to Day 42 (Week 6, Visit 4)	22	-0.05 (0.69)	0.4253	26	-0.17 (0.86)	0.8749	28	0.21 (0.73)	0.0328	29	-0.21 (0.73)
Change from baseline to Day 84 (Week 12, Visit 5)	22	0.11 (0.94)	0.2594	26	0.13 (0.82)	0.1753	28	-0.11 (0.66)	0.7977	29	-0.16 (0.75)

**a** nominal p-value calculated using 2-sided t-test comparing lifitegrast to vehicle. **b** The term vehicle is used throughout this review because it is a more accurate descriptor of the reference product used in this study.

Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining/none; 2=countable/mild; 3=uncountable, but not confluent/moderate; 4= confluent/severe.

Note: Results presented in this table were determined pre-CAE using the Ora scale in the study eye only.

Source: CSR, Section 14, Table 14.2.2.1.2

**Reviewer’s Comment:**

*The post hoc analysis revealed numerical dose-responses for inferior corneal fluorescein staining score in patients who had used artificial tears in the 30 days preceding Visit 1. The 0.1, 1 and 5% lifitegrast groups had nominally significant differences from the vehicle group in the change from baseline to Day 84 (nominal p-values equal to 0.0453, 0.0013, and 0.0002, respectively). Numerical dose responses were also observed for artificial tear users in total corneal staining score.*

*The applicant treated these results as hypothesis generating for the subsequent Phase 3 trials, OPUS-1(1118-KCS-200) and OPUS-2 (1118-DRY-300).*

## 6.2 OPUS-1 (Study 1118-KCS-200)

For the treatment of the signs and symptoms of dry eye disease.

### 6.2.1 Methods

The description of the clinical trial design is contained in Section 5.3.2. Clinical study reports, clinical protocols and literature references were submitted related to the clinical trial in support of the New Drug Application.

### 6.2.2 Demographics

**Table 6.2.2-1 Demographic Characteristics – Safety Population**

Variables		Vehicle N=295	5% LIF N=293
Age (years)	Mean (SD)	61.1 (11.77)	60.2 (12.21)
Sex: n (%)	Male	78 (26.4)	64 (21.8)
	Female	217 (73.6)	229 (78.2)
Race: n (%)	White	276 (93.6)	270 (92.2)
	Black or African American	11 (3.7)	16 (5.5)
	Other	4 (1.4)	3 (1.0)
	Asian	2 (0.7)	3 (1.0)
	American Indian or Alaska Native	2 (0.7)	1 (0.3)
Ethnicity: n (%)	Hispanic or Latino	7 (2.4)	6 (2.0)
	Not Hispanic or Latino	288 (97.6)	287 (98.0)
Iris color: n(%)	Black	0	3 (1.0)
	Blue	98 (33.2)	105 (35.8)
	Brown	96 (32.5)	113 (38.6)
	Hazel	71 (24.1)	52 (17.7)
	Green	27 (9.2)	18 (6.1)
	Gray	2 (0.7)	1 (0.3)
	Other	0	1 (0.3)
History of Artificial Tear Use	With Active Use	129 (43.7)	128 (43.7)
	Without Active Use	166 (56.3)	165 (56.3)
Source: CSR, Section 14, Table 1.2.1			

**Reviewer’s Comment:**

*Patient demographics were well-balanced across the treatment groups at baseline. The majority of subjects did not have a history of active artificial tear use at baseline.*

**Prior and Concomitant Medications**

Overall, 45.7% of subjects took a prior or concomitant ocular medication. The most common (>10%) prior or concomitant medication was carmellose sodium (artificial tear preparation). Overall, most subjects (94.0%) took prior or concomitant non-ocular medications. The most common non-ocular medications (>10%) were multivitamins, ergocalciferol, calcium, omeprazole, fish oil, simvastatin, Lisinopril, paracetamol, ibuprofen, and acetylsalicylic acid.

**6.2.3 Subject Disposition**

A total of 1016 subjects were screened. Of the 588 subjects randomized, 295 subjects were in the vehicle group and 293 were in the lifitegrast 5% group. All subjects received at least 1 dose of an investigational product, therefore, all were included in both the Safety and ITT populations. The Per Protocol population included subjects who completed the study with no major protocol deviations as determined by a masked review. Seventy-seven subjects were excluded from the Per Protocol population, 30 subjects from the vehicle group and 47 subjects from the lifitegrast 5% group.

**Table 6.2.3-1  
Subject Disposition – All Randomized Subjects**

<b>Subject Disposition</b>	<b>Vehicle N=295 n (%)</b>	<b>5% LIF N=293 n (%)</b>
Randomized subjects	295	293
Safety Population <sup>a</sup>	295 (100.0)	293 (100.0)
ITT Population <sup>a</sup>	295 (100.0)	293 (100.0)
Per-Protocol Population <sup>a</sup>	265 (89.8)	146 (84.0)
Completed Study	284 (96.3)	281 (95.9)
Discontinued Study	11 (3.7)	12 (4.1)
<i>Reasons for Discontinuation</i>		
Adverse Event	3 (1.0)	10 (3.4)
Lost to follow-up	2 (0.7)	0
Non-compliance	2 (0.7)	0
Pregnancy	1 (0.3)	0
Other	3 (1.0)	2 (0.7)
Source: CSR Table 3		

<sup>a</sup> Percentages based on randomized subjects.

<sup>b</sup> These subjects had a reason for study withdrawal of adverse event. An additional subject in the vehicle treatment group was withdrawn from treatment, but not the study, due to an adverse event.

**Reviewer’s Comment:**

*The subject completion rate was 96% in each group.*

**Table 6.2.3-2 Subjects Discontinued from Treatment or Study  
Safety Population**

Reason for Discontinuation	Treatment	Subject Number	Study Duration
AE – Periocular dermatitis	Lifitegrast	11-11084	15
AE – Worsening of upper abdominal pain	Lifitegrast	12-12044	43
AE – Pain upon instillation, blurry vision after instillation	Lifitegrast	12-12058	15
AE – Vitreous hemorrhage / retinal tear	Lifitegrast	12-12093	42
AE – Ocular redness	Lifitegrast	13-13046	13
AE – Burning upon instillation, OU	Lifitegrast	15-15027	15
AE – Stinging upon instillation X 15 min	Lifitegrast	15-15042	43
AE – Broken bones	Lifitegrast	15-15051	44
AE – Burning upon instillation	Lifitegrast	20-20066	16
AE – Worsening of multiple sclerosis	Lifitegrast	28-28011	42
AE – Pain OU	Vehicle	11-11120	42
AE – Increased central superficial punctate keratitis OU	Vehicle	14-14001	42
AE – Herniated nucleus pulposus (C7,T1)	Vehicle	15-15002	132
Lost to follow-up	Vehicle	11-11107	21
Lost to follow-up	Vehicle	11-11261	91
Noncompliance	Vehicle	11-11026	50
Noncompliance	Vehicle	11-11039	127
Other –Unable to make visits	Lifitegrast	11-11025	35
Other – Unable to make visits (moving)	Lifitegrast	20-20041	69
Other – Pregnancy	Vehicle	11-11250	86
Other – Unable to make visits	Vehicle	15-15059	44
Other – Withdrew consent	Vehicle	20-20011	47

Source: Study 1118-KCS-200 CSR, Section 16.2.1

**Reviewer’s Comment:**

*The most frequent reasons for discontinuation were adverse reactions related to eye irritation after instillation of lifitegrast 5%.*

**Protocol Deviations**

During the study, 7.8% of vehicle subjects and 13.0% of lifitegrast subjects had a major protocol deviation (Table 6.1.3-3). The most common major protocol deviations were non-compliance with the investigational product as assessed by reconciliation of the used and unused vials and by review of the investigational product diaries, and use of prohibited concomitant medications.

Three subjects in the lifitegrast treatment group (Subjects 11053, 11071, and 28011) had inclusion/exclusion and/or randomization protocol deviations that were deemed major by the sponsor.

- Subject 11053 did not meet inclusion criterion 10.1 (change in inferior corneal fluorescein staining score  $\geq +1$ ) or inclusion criterion 10.3 (STT  $\geq 1$  and  $\leq 10$ mm) in the same eye at Visits 1 and 2.
- Subject 11071 violated exclusion criterion 3 because he had previously received lifitegrast in another clinical study protocol; an exemption was denied, but the subject was randomized.
- Subject 28011 used interferon beta-1a, an immunosuppressive t-cell inhibitor, for Sjögren’s Syndrome since 2004, which violated inclusion criterion 12.

**Table 6.2.3-3  
Major Protocol Deviations – All Randomized Subjects**

<b>Subject Disposition</b>	<b>Vehicle N=295 n (%)</b>	<b>5% LIF N=293 n (%)</b>
n (%)	23 (7.8)	38 (13.0)
Informed consent	0	0
Inclusion/exclusion and randomization	0	3 (1.0)
Investigational product instillation	1 (0.3)	0
Improper protocol procedures	0	0
Site’s failure to report SAE/AE	0	0
Visit out of window	1 (0.3)	0
Non-compliance with investigational product	10 (3.4)	23 (7.8)
Prohibited concomitant medication use	10 (3.4)	13 (4.4)
Failure to follow instructions	2 (0.7)	6 (2.0)
Other	1 (0.3)	0
Source: CSR Table 6		

Note: This table only summarizes protocol deviations that were identified by sites on eCRFs. Protocol deviations identified programmatically (i.e., overall compliance <80% or >120%) are not included.

## 6.2.4 Analysis of Primary Endpoint(s)

**Table 6.2.4-1**  
**Co-Primary Efficacy**  
**Inferior Corneal Staining Score at Day 84 (Sign)**  
**ITT Population with LOCF**

	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Baseline (Day 0)</b>		
n	294 <sup>a</sup>	293
mean (SD)	1.81 (0.599)	1.84 (0.597)
<b>Day 84 (Week 12, Visit 5)</b>		
n	294 <sup>a</sup>	293
mean (SD)	1.98 (0.874)	1.77 (0.879)
<b>Change from Baseline to Day 84</b>		
n	294	293
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

a 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: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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

**Reviewer's Comment:**

*In Study 1118-KCS-200, the lifitegrast treatment group achieved a statistically significant mean decrease from baseline to Day 84 in inferior corneal fluorescein staining score compared to the vehicle treatment group.*

**Sensitivity Analyses**

**Table 6.2.4-2  
Co-Primary Efficacy – Sensitivity Analyses  
Inferior Corneal Staining Score at Day 84 (Sign)**

<b>Change from Baseline to Day 84</b>	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>ITT with Worse observation carried forward (WOCF)</b>		
n	291	287
Mean (SD)	0.18 (0.826)	-0.07 (0.877)
Treatment difference		0.25
95% confidence interval		(0.11, 0.39)
p-value (t-test)		0.0004
<b>Mixed model repeated measures analysis</b>		
n	283	281
Mean (SD)	0.17 (0.813)	-0.08 (0.880)
Treatment difference		0.11
95% confidence interval		(0.02, 0.20)
p-value		0.0133
<b>Per Protocol with Observed Data</b>		
n	265	246
Mean (SD)	0.15 (0.802)	-0.09 (0.872)
Treatment difference		0.23
95% confidence interval		(0.09, 0.38)
p-value (t-test)		0.0017

Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3-uncountable, but not confluent; 4= confluent.

Note: Results presented in this table are from the study eye only.

Source: Section 14, Table 3.1.2.1, Table 3.1.2.2, Table 3.1.2.3.

**Reviewer’s Comment:**

*The results of sensitivity analyses on the primary efficacy sign endpoint with the Worst Observation Carried Forward, ANCOVA Repeated Measures and the Per Protocol populations were consistent primary efficacy analysis.*

**Table 6.2.4-3**  
**Co-Primary Efficacy**  
**Visual-related Function Ocular Surface Disease Index (VR-OSDI) Subscale Score**  
**(Symptom)**  
**ITT Population with LOCF**

	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Baseline (Day 0)</b>		
n	295	293
mean (SD)	0.93 (0.958)	0.86 (0.931)
<b>Day 84 (Week 12, Visit 5)</b>		
n	295	292
mean (SD)	0.80 (0.838)	0.75 (0.861)
<b>Change from Baseline to Day 84</b>		
n	294	293
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: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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

**Sensitivity Analyses**

**Table 6.2.4-4**  
**Co-Primary Efficacy – Sensitivity Analyses**  
**Visual-related Function Ocular Surface Disease Index Subscale Score (Symptom)**

<b>Change from Baseline to Day 84</b>	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Worse observation carried forward (WOCF)</b>		
n	292	286
Mean (SD)	-0.12 (0.761)	-0.11 (0.838)
Treatment difference		-0.02
95% confidence interval		(-0.15, 0.12)
p-value (t-test)		0.8195
<b>Mixed model repeated measures analysis</b>		

<b>Change from Baseline to Day 84</b>	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
n	284	280
Mean (SD)	-0.11 (0.758)	-0.12 (0.834)
Treatment difference		0.01
95% confidence interval		(-0.07, 0.10)
p-value		0.7636
<b>Per Protocol with Observed Data</b>		
n	265	245
Mean (SD)	-0.11 (0.766)	-0.17 (0.832)
Treatment difference		0.06
95% confidence interval		(-0.08, 0.20)
p-value (t-test)		0.4168

Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

Note: Results presented in this table are from the study eye only.

Source: Section 14, Table 3.1.2.1, Table 3.1.2.2, Table 3.1.2.3.

**Reviewer’s Comment:**

*The treatment group difference for the co-primary symptom efficacy endpoint, visual-related function ocular surface disease index subscale score, was not statistically significant. The results of sensitivity analyses utilizing the Worst Observation Carried Forward, ANCOVA Repeated Measures and the Per Protocol populations were consistent with the primary efficacy analysis.*

**6.2.5 Analysis of Secondary Endpoints(s)**

Since statistical significance was not achieved for the symptom co-primary endpoint, the results of the hypothesis tests for the secondary endpoints are provided as descriptive statistics only. Statistical significance cannot be claimed for the secondary endpoints, but nominal p-values are presented as descriptive statistics.

**Table 6.2.5-1  
Secondary Efficacy – Schirmer Tear Test Score  
ITT Population with LOCF**

<b>Schirmer Tear Test Score</b>	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Baseline (Visit 2) (mm/5 minutes)</b>		
n	294	293
Mean (SD)	4.69 (2.855)	4.90 (3.008)

<b>Schirmer Tear Test Score</b>	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Day 14 (Visit 3) (mm/5 minutes)</b>		
Mean (SD)	5.66 (5.074)	5.90 (4.815)
Treatment difference		-0.24
95% confidence interval		(-1.04, 0.56)
p-value (t-test)		0.5550
<b>Day 84 (Visit 5) (mm/5 minutes)</b>		
Mean (SD)	6.26 (5.598)	6.63 (5.772)
Treatment difference		-0.38
95% confidence interval		(-1.30, 0.55)
p-value (t-test)		0.4230

Note: Higher Schirmer Tear Test result indicates more tear production; Results presented are from the study eye only.

**Table 6.2.5-2**  
**Secondary Efficacy – Total Ocular Surface Disease Index Score (Symptom)**  
**ITT Population with LOCF**

	<b>Vehicle N=295</b>	<b>5% LIF N=293</b>
<b>Baseline (Visit 2)</b>		
n	295	293
Mean (SD)	27.05 (18.147)	26.03 (19.042)
<b>Change from Baseline to Day 14 (Visit 3)</b>		
Mean (SD)	-2.34 (14.000)	-1.33 (13.405)
Treatment difference		-1.01
95% confidence interval		(-3.23, 1.21)
p-value (t-test)		0.3731
<b>Change from Baseline to Day 84 (Visit 5)</b>		
Mean (SD)	-3.84 (14.949)	-2.98 (15.250)
Treatment difference		-0.86
95% confidence interval		(-3.31, 1.59)
p-value (t-test)		0.4904

Note: Higher Ocular Surface Disease Index score indicates greater ocular impairment.

**Reviewer's Comment:**

*The nominal p-values for the secondary efficacy endpoints were not significant. The results of sensitivity analyses on these secondary efficacy endpoints with the Worst Observation Carried Forward, ANCOVA Repeated Measures and the Per Protocol populations were consistent.*

### 6.2.6 Other Endpoints

Multiple tertiary efficacy endpoints were assessed. The applicant pre-specified a subgroup analysis of subjects with a history of active artificial tear use versus subjects without a history of active artificial tear use. The applicant noted a potential treatment group difference in the ocular symptom, eye dryness as measured by the VAS scale, in favor of the lifitegrast treatment group in this subgroup.

### 6.2.7 Subpopulations

The efficacy subgroup analysis of subjects with and without a history of active artificial tear use was a pre-specified tertiary efficacy variable. Subgroup analysis of ocular signs (corneal fluorescein staining score, blink rate, conjunctival redness score, tear film break-up time, lissamine staining score, Schirmer Tear Test) and ocular symptoms (Ocular Surface Disease Index Score, ocular discomfort score, visual analogue scale scores for burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia, pain) was performed.

Regarding the ocular signs, the corneal fluorescein staining score, the difference between treatment groups for the inferior region, superior region and total cornea showed numerical improvement favoring the lifitegrast group for both subgroups. The finding was consistent in the ITT with LOCF and the Per Protocol populations. No significant treatment group differences were seen for the subgroup analyses for blink rate, conjunctival redness score, tear film break-up time, lissamine green staining score, or Schirmer Tear Test.

Regarding the ocular symptoms, a potential treatment group difference in ocular discomfort score and in eye dryness as measured by the VAS scale in favor of the lifitegrast treatment group in the subgroup of subjects with a history of active artificial tear use was noted.

The results of a Per Protocol population analysis were consistent with the LOCF subgroup analysis results.

**Reviewer's Comment:**

*The applicant used this information as hypothesis generating for the design of the subsequent Phase 3 safety and efficacy study – 1118-DRY-300 (OPUS-2).*

### 6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

## 6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with latanoprost ophthalmic solution.

### 6.2.10 Additional Efficacy Issues/Analyses

None.

## 6.3 OPUS-2 (Study 1118-DRY-300)

For the treatment of the signs and symptoms of dry eye disease.

### 6.3.1 Methods

The description of the clinical trial design is contained in Section 5.3.3. Clinical study reports, clinical protocols and literature references were submitted related to the clinical trial in support of the New Drug Application.

### 6.3.2 Demographics

**Table 6.3.2-1  
Demographic Characteristics – Randomized Population**

Variables		Vehicle N=360	5% LIF N=358
Age (years)	Mean (SD)	58.9 (14.26)	58.7 (13.93)
	≥ 65 years, n (%)	135 (37.5)	122 (34.1)
	≥ 75 years, n (%)	42 (11.7)	39 (10.9)
Sex: n (%)	Male	95 (26.4)	73 (20.4)
	Female	265 (73.6)	285 (79.6)
Race: n (%)	White	305 (84.7)	303 (84.6)
	Black or African American	34 (9.4)	30 (8.4)
	Asian	14 (3.9)	19 (5.3)
	American Indian or Alaska Native	2 (0.6)	4 (1.1)
	Native Hawaiian or other Pacific Islander	3 (0.8)	2 (0.6)
	Other	2 (0.6)	0
Ethnicity: n (%)	Hispanic or Latino	64 (17.8)	79 (22.1)
	Not Hispanic or Latino	296 (82.2)	279 (77.9)

Variables		Vehicle N=360	5% LIF N=358
Iris color , Study eye: n(%)	Black	0	1 (0.3)
	Blue	86 (23.9)	80 (22.3)
	Brown	189 (52.5)	193 (53.9)
	Hazel	49 (13.6)	56 (15.6)
	Green	35 (9.7)	27 (7.5)
	Gray	1 (0.3)	1 (0.3)
Source: CSR, Section 14, Table 1.2.1			

**Reviewer’s Comment:**

*Patient demographics were well-balanced across the treatment groups at baseline. Unlike the Phase 2 Dry Eye study and OPUS-1, artificial tear use within 30 days of Visit 1 was required for study entry.*

**Table 6.3.2-2  
Randomization Strata – Randomized Population**

	Vehicle N=360 n (%)	5% LIF N=358 n (%)
Inferior corneal staining score ≤ 1.5, eye dryness score < 60	23 (6.4)	23 (6.4)
Inferior corneal staining score ≤ 1.5, eye dryness score ≥ 60	29 (8.1)	31 (8.7)
Inferior corneal staining score >1.5, eye dryness score < 60	99 (27.5)	100 (27.9)
Inferior corneal staining score > 1.5, eye dryness score ≥ 60	209 (58.1)	204 (57.0)
Source: CSR, Section 14, Table 1.6		

Note: A small percentage of subjects were incorrectly stratified at randomization.

**Reviewer’s Comment:**

*The treatment groups were well balanced with regard to the randomization strata at baseline. The majority of subjects had an inferior corneal staining score > 1.5 and eye dryness score ≥ 60.*

**Prior and Concomitant Medications**

Overall, all subjects took a prior ocular medication because subjects were required to use artificial tears within 30 days of screening. Overall, 5.2% of subjects took concomitant medications for ocular health. The most common concomitant medication for ocular health was fish oil with minerals and vitamins (1%). Overall, 9.95 of subjects took prior non-ocular medications. Most subjects (83.8%) took concomitant non-ocular medications. The most common concomitant non-ocular medications (>10%) were acetylsalicylic acid, viterra (vitamins), cholecalciferol, and fish oil.

### 6.3.3 Subject Disposition

A total of 1455 subjects were screened, and 557 subjects did not enter the Vehicle Run-in Period due to screening failure. A further 178 subjects were not randomized after the Vehicle Run-in Period due to screening failure. Two randomized subjects were excluded because they were duplicate subjects (same subject randomized twice), resulting in a total of 718 unique randomized subjects (vehicle: 360 subjects; lifitegrast: 358 subjects). The ITT population and Safety Populations included all unique randomized subjects who received at least one dose of investigational product. All of these subjects were also included in the Safety population.

As previously mentioned, two subjects were excluded from the Randomized Population because their records represented a second randomization for the same subject. Data for the duplicate subjects are included in the efficacy and safety analyses by the first randomized treatment assignment only, but data from both randomizations are included in listings. Subject 56-005 entered the study a second time as Subject 57-041. Subject 56-037 entered the study a second time as Subject 79-016. Thus, data from Subjects 57-041 and 79-016 are not included in efficacy and safety analyses, and are only included in listings. Subject 56-030 entered the study a second time as Subject 79-026, but was deemed a screen failure prior to randomization. Duplicate subjects are listed in Appendix 16.2, Listing 1.2 of the CSR. Additionally, two subjects were deemed screen failures, but were later re-screened and randomized with different subject numbers. The total screening count of 1455 subjects includes 1450 unique subjects.

Also of note, Subject 78-006 was assigned to the vehicle group, but received lifitegrast via an incorrect kit at Visit 3 and was discontinued from the study (refer to the CSR, Appendix 16.2, Listing 1.1). This subject was included in the lifitegrast group for the Safety Population, but in the vehicle group for the Randomized and ITT Populations.

**Table 6.3.3-1  
Subject Disposition – All Randomized Subjects**

	<b>Vehicle N=295 n (%)</b>	<b>5% LIF N=293 n (%)</b>	<b>Total N=718 n (%)</b>
Screened subjects <sup>a</sup>			1455
Number of subjects not starting Vehicle Run-in Period			557
Number of subjects not randomized after Vehicle Run-in Period			178
Number of subjects randomized			720
Excluded from data analysis because records represent second randomization for a subject			2
Included in data analysis			718
Randomized subjects	360	358	718
Safety Population <sup>b, c</sup>	359 (99.7)	359 (100.3) <sup>c</sup>	718 (100.0)
ITT Population <sup>b</sup>	360 (100.0)	358 (100.0)	718 (100.0)

	<b>Vehicle N=295 n (%)</b>	<b>5% LIF N=293 n (%)</b>	<b>Total N=718 n (%)</b>
Completed Study <sup>b</sup>	348 (96.7)	321 (89.7)	669 (93.2)
Withdrew from Study <sup>b</sup>	12 (3.3)	37 (10.3)	49 (6.8)
<i>Reasons for Withdrawal<sup>b</sup></i>			
Adverse Event <sup>b</sup>	3 (0.8)	26 (7.3)	29 (4.0)
Lost to follow-up <sup>b</sup>	0	2 (0.6)	2 (0.3)
Non-compliance <sup>b</sup>	0	1 (0.3)	1 (0.1)
Other <sup>b</sup>	9 (2.5)	8 (2.2)	17 (2.4)
Source: CSR Table 3			

a The total screening count of 1455 subjects includes 1450 unique subjects.

b Percentages based on Randomized Population.

c Subjects are categorized by actual treatment received, even if randomized to the other treatment. Subject 78-006 was assigned to the vehicle group, but received lifitegrast via an incorrect kit at Day 14 (Week 2, Visit 3) and was discontinued from the study. This subject was included in the lifitegrast group for the Safety Population, but in the vehicle group for the Randomized and ITT populations.

**Reviewer’s Comment:**

*The subject completion rate was 97% in the vehicle group to 90% in the 5% lifitegrast group. The most frequent reason for discontinuation in the lifitegrast group was adverse event which was experienced by 7% of the 5% lifitegrast group (0.8% of the vehicle group).*

**Table 6.3.3-2 Subjects Discontinued from Treatment or Study  
Safety Population**

<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
AE – Ocular redness	Lifitegrast	51-132	7
AE – Ocular burning	Lifitegrast	53-001	25
AE – Ocular burning OU	Lifitegrast	53-067	40
AE – Ocular burning	Lifitegrast	54-017	13
AE – Epithelial defect with underlying infiltrate	Lifitegrast	54-019	42
AE – Decreased visual acuity	Lifitegrast	55-003	14
AE – Burning upon instillation	Lifitegrast	56-027	37
AE – Dermatitis	Lifitegrast	57-025	74
AE – Nosebleed	Lifitegrast	57-036	70
AE – Angular blepharitis	Lifitegrast	57-040	52
AE – Nightmares, itching, burning, dysgeusia	Lifitegrast	59-007	14
AE – Moderate dermatitis, upper and lower eyelids	Lifitegrast	59-022	76
AE – Eye pain in temple area	Lifitegrast	61-029	24

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<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
AE – Photophobia after instillation	Lifitegrast	63-027	42
AE – Allergic conjunctivitis, increased ocular dryness	Lifitegrast	65-101	7
SAE – Hospitalization for removal of renal carcinoma	Lifitegrast	65-145	57
AE – Corneal abrasion, corneal foreign body	Lifitegrast	65-187	5
AE – Severe continuous burning	Lifitegrast	69-026	2
AE – Ocular burning upon instillation	Lifitegrast	70-011	7
AE – Blurred vision	Lifitegrast	70-049	17
AE – Tearing	Lifitegrast	70-059	10
AE – Burning, blurred vision, increased dryness	Lifitegrast	73-010	10
AE – Blurred vision upon instillation, temporal pain	Lifitegrast	77-002	1
AE – Skin rash	Lifitegrast	77-019	44
AE – Burning upon instillation, photophobia, eye pain	Lifitegrast	77-038	9
AE – Foggy vision, toe pain, pain upon instillation	Lifitegrast	79-029	2
AE – Ocular hyperemia OD	Vehicle	56-029	44
AE – Bilateral degenerative changes in hip joint	Vehicle	59-023	55
AE – Corneal ulcer	Vehicle	78-012	15
Lost to follow-up	Lifitegrast	63-062	45
Lost to follow-up	Lifitegrast	73-034	21
Noncompliance	Lifitegrast	73-028	15
Other – Personal/family issues	Lifitegrast	55-008	58
Other	Lifitegrast	56-019	57
Other – Did not complete study	Lifitegrast	56-028	71
Other – Withdrew consent	Lifitegrast	65-181	42
Other – Insufficient duration of treatment	Lifitegrast	69-023	68
Other – Insufficient duration of treatment	Lifitegrast	69-025	71
Other – Personal reason	Lifitegrast	77-034	2
Other – Insufficient duration of treatment	Lifitegrast	78-052	71
Other – Inappropriately enrolled <sup>a</sup>	Lifitegrast	79-016	70
Other – Lack of efficacy	Vehicle	53-040	24
Other – Unplanned travel	Vehicle	56-022	57
Other – Withdrew consent	Vehicle	58-023	49
Other – Financial / IRS concerns	Vehicle	62-026	27

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Reason for Discontinuation	Treatment	Subject Number	Study Duration
Other – Withdrew consent, unplanned travel	Vehicle	65-167	85
Other – Insufficient duration of treatment	Vehicle	68-046	71
Other – Insufficient duration of treatment	Vehicle	69-021	71
Other – Lack of efficacy	Vehicle	73-019	42
Other – Protocol deviation; given incorrect kit	Vehicle	78-006	42

Source: Study 1118-DRY-300 CSR, Section 16.2.1

a Subject identified as duplicate subject, randomized twice in the study using a different subject number.

### Reviewer’s Comment:

*The most frequent reasons for discontinuation were adverse reactions related to eye irritation after instillation of lifitegrast 5%.*

### Protocol Deviations

During a masked review of the data prior to database lock and unmasking, the applicant reviewed the protocol deviations captured on the eCRF. Most of the reported deviations were determined to be minor, i.e., not affecting the efficacy or safety assessments of study subjects.

**Table 6.3.3-3  
Protocol Deviations Reported - Overall  
Randomized Population**

	Vehicle N=360 n (%)	5% LIF N=358 n (%)
Subjects with any deviation	286 (79.4)	287 (80.2)
Informed consent	46 (12.8)	56 (15.6)
Inclusion/exclusion and randomization	42 (11.7)	37 (10.3)
Test article/drug instillation and assignment at site	21 (5.8)	31 (8.7)
Improper protocol procedures at site	25 (6.9)	35 (9.8)
Site’s failure to report SAE/AE	0	0
Visit out of window	36 (10.0)	31 (8.7)
Non-compliance with test article/ study drug	222 (61.7)	227 (63.4)
Use of prohibited concomitant medication	20 (5.6)	16 (4.5)
Failure to follow instructions	13 (3.6)	4 (1.1)
Other	5 (1.4)	5 (1.4)
Incorrect VAS form used	24 (6.7)	17 (4.7)

Source: CSR Section 14, Table 1.5.2

Note: Percentages are based on the number of subjects randomized.

### 6.3.4 Analysis of Primary Endpoint(s)

**Table 6.3.4-1  
Co-Primary Efficacy  
Inferior Corneal Staining Score (Sign)  
ITT Population with LOCF**

	<b>Vehicle N=360</b>	<b>5% LIF N=358</b>
<b>Baseline (Day 0)</b>		
n	360	358
mean (SD)	2.40 (0.722)	2.39 (0.763)
<b>Day 84 (Week 12, Visit 5)</b>		
n	360	358
mean (SD)	1.69 (1.010)	1.66 (1.044)
<b>Change from Baseline to Day 84</b>		
n	360	358
Mean (SD)	-0.71 (0.943)	-0.73 (0.926)
Treatment effect (SE)		0.03 (0.067)
95% confidence interval		(-0.10, 0.17)
p-value (t-test)		0.6186

a ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. Note: Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

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.

**Reviewer’s Comment:**

*In Study 1118-DRY-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.*

*The results of all sensitivity analyses on the inferior corneal staining score co-primary efficacy endpoint were consistent with the above results.*

**Table 6.3.4-3**  
**Co-Primary Efficacy**  
**Eye Dryness Score (Visual Analogue Scale, Symptom)**  
**ITT Population with LOCF**

	<b>Vehicle N=360</b>	<b>5% LIF N=358</b>
<b>Baseline (Day 0)</b>		
n	360	358
mean (SD)	69.22 (16.761)	69.68 (16.954)
<b>Day 84 (Week 12, Visit 5)</b>		
n	360	358
mean (SD)	46.47 (29.875)	34.39 (27.862)
<b>Change from Baseline to Day 84</b>		
n	360	358
Mean (SD)	-22.75 (28.600)	-35.30 (28.400)
Treatment effect (SE)		12.613 (2.085)
95% confidence interval		(8.51, 16.70)
p-value (t-test)		<0.001

a ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size. Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 2=countable; 3=uncountable, but not confluent; 4= confluent.

Note: Results presented in this table are from the study eye only.

Source: Section 14, Table 3.1.1.2

**Reviewer’s Comment:**

*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.*

*The results of sensitivity analyses for the eye dryness score co-primary efficacy endpoint were consistent with the above results.*

**6.3.5 Analysis of Secondary Endpoints(s)**

Since statistical significance was not achieved for the sign co-primary endpoint, the results of the hypothesis tests for the secondary endpoints are not presented. General trends seen with secondary endpoints are presented below.

The lifitegrast and vehicle groups had similar mean improvements from baseline to Day 84 in the objective parameters of total corneal fluorescein staining and nasal conjunctival lissamine green staining in the study eye.

The lifitegrast group showed numerically greater mean improvement from baseline to Day 84 in the subjective parameters of eye discomfort score and ocular discomfort score.

**Reviewer's Comment:**

*The numerical trends of the results for the other sign and symptom secondary efficacy endpoints were consistent with the co-primary efficacy endpoints.*

**6.3.6 Other Endpoints**

Not applicable.

**6.3.7 Subpopulations**

No meaningful differences were seen for the subgroups, and the results were consistent with the primary analysis.

**6.3.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

Not applicable.

**6.3.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with latanoprost ophthalmic solution.

**6.3.10 Additional Efficacy Issues/Analyses**

None.

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

##### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

**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
<b>Phase 1</b>				
<b>Study SAR 1118-001</b>  PK and Safety	Randomized, double-masked, vehicle-controlled dose-escalation study	Lifitegrast 0.1, 0.3, 1, 5% or vehicle ophthalmic solution  <b>28 healthy subjects</b> (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
<b>Phase 2</b>				
<b>Study 1118-ACJ-100</b>  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  <b>60 subjects with allergic conjunctivitis</b> (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)  <b>230 subjects with dry eye disease</b> (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)
<b>Phase 3</b>				
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  <b>588 subjects</b> (142 males/ 446 females)	Single eye 1 drop BID for 84 days (12 weeks)	Copriary 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  <b>718 subjects</b> (168 males/ 550 females)	Single eye 1 drop BID for 84 days (12 weeks)	Copriary 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  <b>332 subjects with dry eye disease</b> (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

**Reviewer's Comment:**

*The safety data obtained from Study SAR 1118-001 in healthy subjects and Study 1118-ACJ-100 in allergic conjunctivitis patients are not presented in the pooled analysis because the dosing regimens and populations differed from the dry eye disease studies.*

### 7.1.2 Categorization of Adverse Events

*The routine clinical testing required to establish the safety of topical ophthalmic drops were adequately addressed in the design and conduct of this clinical trial.*

*All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.*

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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 All Dry Eye Studies Pool was used for the presentation of exposure and overall safety results. 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 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.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

#### Phase 1 Study

During the Phase 1 study, 20 subjects received at least 1 dose of lifitegrast (5 subjects per dose strength [0.1, 0.3, 1, and 5%]). All 20 subjects received every planned dose within their assigned dose strength cohort (0.1, 0.3, 1, or 5%): 1 drop of lifitegrast in 1 eye on Day 1 (1 drop of vehicle in other eye), 1 drop of randomized investigational product in each eye twice daily on Days 5-14, and 1 drop of randomized investigational product in each eye 3 times daily on Days 18-27. Each subject was exposed to lifitegrast for a total of 21 days at varying doses.

Baseline demographic characteristics were similar between treatment groups. Subjects' age ranged from 19-47 years, with the mean age (standard deviation) being 30.5 years (8.9). All subjects were male, and the majority of subjects were Hispanic (89%).

Phase 2 Allergic Conjunctivitis Study

During the Phase 2 allergic conjunctivitis study, 45 subjects received at least 1 dose of lifitegrast (15 subjects per dose strength [0.1, 1, and 5%]). The mean duration of treatment exposure was similar between treatment groups; each treatment group had a median exposure of 13 days.

Subjects' age ranged from 19-75 years, with the mean (standard deviation) being 40.95 years (14.019). The lifitegrast 5% group had a higher mean age (45.33 years) than the lifitegrast 0.1% and 1% groups (41.67 and 37.67 years, respectively) and the vehicle group (39.13 years). The majority of subjects in each treatment group were white (95%) and not Hispanic (91.7%).

12-Week Dry Eye Studies Pool

**Table 7.2.1-1  
Summary of Treatment Exposure – 12-Week Dry Eye Studies Pool <sup>c</sup>  
Safety Population**

	<b>Vehicle N=712</b>	<b>All LIF N=710</b>
Total duration of treatment exposure (days) <sup>a</sup>		
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 (%) <sup>b</sup>		
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

<sup>a</sup> Total treatment exposure is from first randomized masked study treatment to last.

<sup>b</sup> One month is 30.4375 days. The last category of at least 12 months is defined as at least 355 days based on the planned visit at Day 360 with a visit window of 5 days for SONATA.

<sup>c</sup> 12 Week Dry Eye Studies Pool (Phase 2, OPUS-1, and OPUS-2 Studies)

**Reviewer's Comment:**

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

**Table 7.2.1-2**  
**Summary of Demographic and Baseline Characteristics – 12-Week Dry Eye Studies Pool <sup>a</sup>**  
**Safety Population**

	<b>Vehicle N=712</b>	<b>All LIF N=710</b>
Age (years)		
Mean (SD)	59.9 (13.21)	59.6 (13.13)
Median	61.0	59.5
Min, max	19, 89	19, 97
< 65 years, n(%)	443 (62.2)	465 (65.5)
≥ 65 years, n(%)	269 (37.8)	245 (34.5)
< 75 years, n(%)	626 (87.9)	618 (87.0)
≥ 75 years, n(%)	86 (12.1)	92 (13.0)
Sex, n(%)		
Male	186 (26.1)	148 (20.8)
Female	526 (73.9)	562 (79.2)
Ethnicity, n(%)		
Hispanic or Latino	70 (9.8)	86 (12.1)
Not Hispanic or Latino	642 (90.2)	624 (87.9)
Race, n(%)		
White	634 (89.0)	627 (88.3)
Non-White	78 (11.0)	83 (11.7)

Source: CSR, Module 2.7.4, Table 17  
a 12 Week Dry Eye Studies Pool (Phase 2, OPUS-1, and OPUS-2 Studies)

**Reviewer’s Comment:**

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

**SONATA Study**

A total of 504 subjects were screened. Of the 332 subjects randomized, 111 subjects were in the vehicle group and 221 were in the lifitegrast 5% group. One subject (Subject 41-032) was erroneously randomized (lifitegrast group), but never received investigational product.

**Table 7.2.1-3  
Summary of Treatment Exposure  
SONATA Study – Safety Population**

	<b>Vehicle N=111</b>	<b>5% LIF N=220</b>
Duration of treatment exposure (days), mean (SD) <sup>a</sup>	311.3 (114.29)	304.4 (112.50)
Duration of treatment exposure, n (%) <sup>b</sup>		
> 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

<sup>a</sup> Total treatment exposure is from first randomized masked study treatment to last randomized masked study treatment. <sup>b</sup> One month is 30.4375 (365.25/12) days. The last category of at least 12 months is defined as at least 355 days based on the planned visit at Day 360 (Month 12, Visit 7) with a visit window of 5 days.

**Table 7.2.1-4  
Subject Disposition – SONATA Study**

<b>Subject Disposition</b>	<b>Vehicle N=111 n (%)</b>	<b>5% LIF N=221 n (%)</b>	<b>Total N=332 n (%)</b>
Screened subjects <sup>a</sup>			504
Randomized subjects	111	221	332
Safety Population <sup>b</sup>	111 (100.0)	220 (99.5)	331 (99.7)
Subjects who completed study <sup>b</sup>	92 (82.9)	170 (76.9)	262 (78.9)
Subjects who discontinued study <sup>b</sup>	19 (17.1)	51 (23.1)	70 (21.1)
<i>Reasons for Discontinuation <sup>b</sup></i>			
Adverse Event	9 (8.1)	27 (12.2)	36 (10.8)
Death	1 (0.9)	0	1 (0.3)
Lost to follow-up	6 (5.4)	11 (5.0)	17 (5.1)
Non-compliance	2 (1.8)	1 (0.5)	3 (0.9)
Erroneously admitted <sup>c</sup>	0	1 (0.5)	1 (0.3)
Other	1 (0.9)	11 (5.0)	12 (3.6)

Source: SONATA CSR, Table 3

a Number may reflect multiple screenings for the same subject

b Percentages based on Randomized Population

c Subject 41-032 was randomized in error but did not receive investigational product and is not included in the Safety Population.

**Reviewer’s Comment:**

*The subject completion rate was 80% in the 5% lifitegrast group and 83% in the vehicle groups.*

**Table 7.2.1-5  
Demographic Characteristics – SONATA Study  
Randomized Population**

Variables		Vehicle N=111	5% LIF N=221
Age (years)	Mean (SD)	61.0 (13.18)	58.8 (12.39)
	Median	61.3	59.3
	Min, max	24, 89	21, 86
	≥ 65 years, n (%)	41 (36.9)	69 (31.2)
	≥ 75 years, n (%)	15 (13.5)	19 (8.6)
Sex: n (%)	Male	26 (23.4)	56 (25.3)
	Female	85 (76.6)	165 (74.7)
Race: n (%)	White	92 (82.9)	176 (79.6)
	Black or African American	14 (2.6)	31 (14.0)
	Asian	5 (4.5)	11 (5.0)
	Native Hawaiian or other Pacific Islander	0	2 (0.9)
	Other	0	1 (0.5)
Ethnicity: n (%)	Hispanic or Latino	17 (15.3)	33 (14.9)
	Not Hispanic or Latino	94 (84.7)	188 (85.1)
Source: SONATA CSR, Table 4			

**Reviewer’s Comment:**

*Patient demographics were well-balanced across the treatment groups at baseline. The majority of subjects were female, not Hispanic or Latino, and white.*

**Table 7.2.1-6 Subjects Discontinued from Treatment or Study  
SONATA Study – Safety Population**

<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
AE – Headaches	Lifitegrast	31-002	91
AE – Blurred vision after study medication dosage	Lifitegrast	31-013	175
AE – Vertigo	Lifitegrast	32-008	206
AE – Peripheral neuropathy	Lifitegrast	32-010	313
AE – Metallic taste post dose	Lifitegrast	34-025	91
AE – Stinging upon instillation	Lifitegrast	34-026	42
AE – Blurred vision and stinging upon instillation	Lifitegrast	37-003	246
AE – Itchy, watery eyes	Lifitegrast	39-002	303
AE – Corneal erosion	Lifitegrast	39-014	184
AE – Increased tearing, blurred vision	Lifitegrast	40-022	35
AE – Allergic conjunctivitis	Lifitegrast	41-010	71
AE – Worsening visual acuity	Lifitegrast	41-023	14
AE – Depression	Lifitegrast	41-026	168
AE – Dysgeusia	Lifitegrast	41-052	89
AE – Burning sensation	Lifitegrast	42-017	175
AE – Burning upon instillation	Lifitegrast	42-026	43
AE – Pulmonary fibrosis	Lifitegrast	43-005	175
AE – Blurred vision upon instillation	Lifitegrast	43-008	15
AE – Excessive tearing	Lifitegrast	43-016	91
AE – Blurred vision upon instillation	Lifitegrast	44-005	37
AE – Taste perversion upon instillation	Lifitegrast	44-009	84
AE – Worsening superficial punctate keratitis, decreased visual acuity, hyperemia	Lifitegrast	45-001	49
AE – Worsening anterior basement membrane dystrophy	Lifitegrast	45-040	86
AE – Loss of 30 ETDRS letters from baseline	Lifitegrast	45-042	46
AE – Severe blurred vision upon instillation	Lifitegrast	46-032	93
AE – Severe foreign body sensation	Lifitegrast	92-011	170
AE – Tearing	Vehicle	32-022	133
AE – Amaurosis	Vehicle	33-002	35
AE – Burning and tearing upon instillation	Vehicle	37-001	2
AE – Death	Vehicle	38-004	53

<b>Reason for Discontinuation</b>	<b>Treatment</b>	<b>Subject Number</b>	<b>Study Duration</b>
AE – Back pain S/P MVA	Vehicle	38-008	87
AE – Burning and stinging upon instillation	Vehicle	40-001	114
AE – Worsening of dry eye	Vehicle	43-017	64
AE – Disk herniation	Vehicle	44-002	391
AE – Blurred vision	Vehicle	45-013	69
AE – Nasal bleeding	Vehicle	90-015	366
Lost to follow-up	Lifitegrast	36-003	232
Lost to follow-up	Lifitegrast	37-010	342
Lost to follow-up	Lifitegrast	41-003	37
Lost to follow-up	Lifitegrast	41-030	176
Lost to follow-up	Lifitegrast	41-035	213
Lost to follow-up	Lifitegrast	41-045	106
Lost to follow-up	Lifitegrast	41-046	229
Lost to follow-up	Lifitegrast	42-045	335
Lost to follow-up	Lifitegrast	43-006	279
Lost to follow-up	Lifitegrast	45-041	350
Lost to follow-up	Vehicle	35-004	102
Lost to follow-up	Vehicle	41-033	195
Lost to follow-up	Vehicle	41-034	289
Lost to follow-up	Vehicle	41-041	106
Lost to follow-up	Vehicle	42-048	19
Lost to follow-up	Vehicle	92-021	210
Noncompliance	Lifitegrast	45-019	327
Noncompliance	Vehicle	36-004	17
Noncompliance	Vehicle	45-014	100
Other – Unable to make visits	Lifitegrast	32-016	175
Other – Unable to make visits (moving)	Lifitegrast	32-018	85
Other – Lack of efficacy	Lifitegrast	34-014	175
Other – Lack of efficacy	Lifitegrast	35-008	175
Other – Withdrew consent	Lifitegrast	39-016	140
Other – Withdrew consent	Lifitegrast	40-005	178
Other – Family illness, moving	Lifitegrast	40-008	68
Other – Withdrew consent	Lifitegrast	40-018	36
Other – Unable to make visits	Lifitegrast	40-021	259
Other – Unable to make visits	Lifitegrast	40-026	6
Other – Erroneously admitted	Lifitegrast	41-032	---
Other – Unable to keep scheduled visit	Lifitegrast	45-010	333

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Reason for Discontinuation	Treatment	Subject Number	Study Duration
Other – Unable to cost of travel	Vehicle	37-004	95

Source: SONATA CSR, Section 16.2.1

**Reviewer’s Comment:**

*The most frequent reasons for discontinuation were adverse reactions related to eye irritation after instillation of lifitegrast 5%.*

**7.2.2 Explorations for Dose Response**

Lifitegrast ophthalmic solution was administered in multiple dosage regimens. The highest dose tested during the clinical development was lifitegrast 5% three times daily. Adequate dose response information was obtained for the indication.

**7.2.3 Special Animal and/or In Vitro Testing**

*None.*

**7.2.4 Routine Clinical Testing**

*The routine clinical testing required to evaluate the safety concerns of lifitegrast ophthalmic solution 5% was adequately addressed in the design and conduct of this clinical trial. See Section 7.4.2 and 7.4.3 of this review.*

**7.2.5 Metabolic, Clearance, and Interaction Workup**

*Systemic absorption was low. No interaction studies were conducted.*

**7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

*None.*

**7.3 Major Safety Results**

**7.3.1 Deaths**

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.

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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
Arrythmia	SONATA	38-004 68/F	Vehicle	54 days	Hypertension, COPD, sleep apnea

### 7.3.2 Nonfatal Serious Adverse Events

#### Phase 1 Study

No subject experienced a serious adverse event during the Phase 1 study.

#### Phase 2 Allergic Conjunctivitis Study

There was one serious adverse event during this study. Subject 001-1027, a 55 year old male in the vehicle treatment group, had a serious, moderate traumatic hematoma on his right leg which required hospitalization.

#### 12-Week Dry Eye Studies Pool

**Table 7.3.2-1  
Serious Treatment Emergent Adverse Events – 12-Week Dry Eye Studies Pool  
Safety Population**

Study	Subject Number	Treatment Group	Preferred Term
Phase 2 dry eye	002-1174	Vehicle	Asthma
Phase 2 dry eye	002-1195	Lifitegrast 0.1%	Oxygen saturation decreased
Phase 2 dry eye	002-1199	Lifitegrast 0.1%	Hip fracture
Phase 2 dry eye	001-1125	Lifitegrast 1%	Cardiac arrest
OPUS-1	15-15002	Vehicle	Intervertebral disc protrusion
OPUS-1	20-20057	Vehicle	Prostate cancer
OPUS-1	12-12044	Lifitegrast 5%	Abdominal pain, upper
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-1	15-15051	Lifitegrast 5%	Humerus fracture
OPUS-2	50-052	Vehicle	Cerebrovascular accident
OPUS-2	58-001	Vehicle	Bladder cancer
OPUS-2	65-183	Vehicle	Osteoarthritis
OPUS-2	66-031	Vehicle	Colitis ischemic
OPUS-2	63-071	Lifitegrast 5%	Vertigo
OPUS-2	65-145	Lifitegrast 5%	Renal cancer
OPUS-2	73-034	Lifitegrast 5%	Thyrotoxic crisis

Source: CSR, Module 2.7.4 Table 37

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.

Note: The Phase 2 dry eye study used MedDRA Version 11.0. The OPUS-1 and OPUS-2 studies used MedDRA Version 14.1.

**Reviewer’s Comment:**

*Approximately one percent of subjects in the lifitegrast and vehicle treatment groups experienced a serious adverse event. No patterns or safety concerns were raised by the reported adverse events.*

**Table 7.3.2-2  
Serious Treatment Emergent Adverse Events – SONATA Study  
Safety Population**

Subject Number	Treatment Group	Preferred Term
38-004	Vehicle	Arrhythmia
38-008	Vehicle	Spinal fracture
44-002	Vehicle	Intervertebral disc protrusion
45-002	Vehicle	Chronic obstructive pulmonary disease
45-004	Vehicle	Chest pain
45-014	Vehicle	Chronic obstructive pulmonary disease
32-008	Lifitegrast 5%	Hip fracture
38-014	Lifitegrast 5%	Myocardial infarction
39-002	Lifitegrast 5%	Syncope, atrioventricular block
41-020	Lifitegrast 5%	Rheumatoid arthritis
41-051	Lifitegrast 5%	Osteoarthritis
45-019	Lifitegrast 5%	Dysmenorrhea
45-026	Lifitegrast 5%	Colonic polyp
46-003	Lifitegrast 5%	Urinary tract infection, pneumonia
48-004	Lifitegrast 5%	Back pain, transient ischemic attack

Source: CSR, Module 2.7.4 Table 39

Note: The SONATA study used MedDRA Version 14.1.

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.

**Reviewer’s Comment:**

*The serious adverse events reported were considered not related to the investigational product and common in the age group studied. 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.*

### 7.3.3 Dropouts and/or Discontinuations Not Previously Described

#### Phase 1 Study

No subject was prematurely discontinued from the Phase 1 study due to a treatment emergent adverse event.

#### Phase 2 Allergic Conjunctivitis Study

**Table 7.3.3-1  
Reasons for Discontinuation – Phase 2 Allergic Conjunctivitis Study  
Safety Population**

<b>Subject Disposition</b>	<b>0.1% LIF N=15 n (%)</b>	<b>1% LIF N=15 n (%)</b>	<b>5% LIF N=15 n (%)</b>	<b>Vehicle N=15 n (%)</b>
Randomized subjects	15 (100.0)	15 (100.0)	15 (100.0)	15 (100.0)
Subjects who completed study	13 (86.7)	13 (86.7)	21 (80.0)	13 (86.7)
Subjects who discontinued from study	2 (13.3)	2 (13.3)	3 (20.0)	2 (13.3)
<i>Primary reason for withdrawal</i>				
Adverse Event	0	1 (6.7)	2 (13.3)	1 (6.7)
Erroneously enrolled or did not meet entry criteria	1 (6.7)	0	0	0
Non-compliance	1 (6.7)	1 (6.7)	1 (6.7)	1 (6.7)

Source: CSR, Module 2.7.4, Table 9

Note: The Randomized Population, Safety Population, and ITT Population were identical for the Phase 2 allergic conjunctivitis study.

#### **Reviewer’s Comment:**

*The subject completion rate ranged from 95% in the 0.1% lifitegrast group to 83% in the 5% lifitegrast and vehicle groups.*

**Table 7.3.3-2  
Subjects Discontinued due to an Adverse Event  
Phase 2 Allergic Conjunctivitis Study  
Safety Population**

<b>Subject Number</b>	<b>Treatment Group</b>	<b>Reason for Discontinuation</b>
001-1023	Vehicle	Food poisoning, diarrhea, upper abdominal pain, arthralgia, myalgia, chills
001-1034	Lifitegrast 1%	Moderate eyelid and conjunctival edema
001-1021	Lifitegrast 5%	Moderate keratitis, mild corneal neovascularization OU
001-1053	Lifitegrast 5%	Moderate corneal abrasion

### 7.3.4 Significant Adverse Events

Refer to Section 7.4.1 for Common Adverse Events. No other significant adverse events were identified.

### 7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns were identified for the submission.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

**Table 7.4.1-1**  
**Treatment Emergent Adverse Events Occurred in >1% in Either Treatment Group**  
**All Dry Eye Studies Pool<sup>a</sup> – Safety Population**

System Organ Class Preferred Term	Vehicle N=823 n (%)	All LIF N=1044 n (%)
<b>Ocular TEAEs</b>		
Subjects with $\geq 1$ ocular TEAE	187 (22.7)	493 (47.2)
Eye disorders	135 (16.4)	262 (25.1)
Visual acuity reduced	48 (5.8)	66 (6.3)
Vision blurred	10 (1.2)	33 (3.2)
Lacrimation increased	4 (0.5)	29 (2.8)
Eye irritation	5 (0.6)	25 (2.4)
Eye pain	6 (0.7)	23 (2.2)
Eye pruritus	8 (1.0)	19 (1.8)
Ocular hyperemia	6 (0.7)	17 (1.6)
Conjunctival hemorrhage	4 (0.5)	12 (1.1)
Conjunctival hyperemia	10 (1.2)	12 (1.1)
Dry eye	11 (1.3)	9 (0.9)
General disorders and administration site conditions	55 (6.7)	308 (29.5)
Instillation site pain	25 (3.0)	139 (13.3)
Instillation site irritation	22 (2.7)	130 (12.5)
Instillation site reaction	8 (1.0)	113 (10.8)
Instillation site pruritus	7 (0.9)	34 (3.3)
Instillation site foreign body sensation	2 (0.2)	11 (1.1)
Instillation site lacrimation	2 (0.2)	11 (1.1)
<b>Non-ocular TEAEs</b>		
Subjects with $\geq 1$ non-ocular TEAE	184 (22.4)	355 (34.0)

System Organ Class Preferred Term	Vehicle N=823 n (%)	All LIF N=1044 n (%)
Infections and Infestations	80 (9.7)	87 (8.3)
Nasopharyngitis	32 (3.9)	32 (3.1)
Sinusitis	9 (1.1)	12 (1.1)
Urinary tract infection	8 (1.0)	8 (0.8)
Nervous system disorders	23 (2.8)	175 (16.8)
Dysgeusia	3 (0.4)	143 (13.7)
Headache	6 (0.7)	25 (2.4)

Source: CSR, Module 2.7.4 Table 28

a All Dry Eye Studies Pool includes the Phase 2 Dry Eye Study, OPUS-1, OPUS-2 and SONATA studies.

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.

### Reviewer's Comment:

*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 (14%), instillation site pain (13%), instillation site irritation (13%), instillation site reaction (11%), and visual acuity reduced (6%).*

*The treatment emergent adverse reactions which occurred in between 1% and 5% of subjects and more frequently in the lifitegrast group compared to the vehicle group were: instillation site pruritus (3%), lacrimation increased (3%), vision blurred (3%), eye irritation (2%), eye pain (2%), eye pruritus (2%), headache (2%), ocular hyperemia (2%), conjunctival hemorrhage (1%), instillation site foreign body sensation (1%), and instillation site lacrimation (1%).*

## 7.4.2 Laboratory Findings

Clinical laboratory evaluations were only conducted in the Phase 1 study and as part of a substudy in the SONATA study. During the Phase 1 (healthy volunteer) and SONATA studies, the changes in clinical chemistry, hematology, and urinalysis results, lymphocyte counts, and corneal endothelial cell counts (SONATA only) were minimal and similar between treatment groups. There was no evidence of lymphocyte or neutrophil suppression.

## 7.4.3 Vital Signs

Vital signs were only collected during the Phase 1 study. There were no clinically meaningful changes from baseline in vital signs during the study.

## 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were only performed in the Phase 1 study. No clinically meaningful changes from baseline in electrocardiogram results were observed during the study.

## 7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this product.

## 7.4.6 Immunogenicity

Immunogenicity testing was not performed during the clinical development of lifitegrast.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Lifitegrast ophthalmic solution was evaluated at multiple dose levels during clinical development. Irritation at the site of instillation was dose dependent.

### 7.5.2 Time Dependency for Adverse Events

Lifitegrast does not have a delayed onset of action. Exploration of time to onset was not conducted.

### 7.5.3 Drug-Demographic Interactions

Analyses by age, sex and race were performed on the 12-Week Dry Eye Studies Pool. The overall safety profile was consistent across age, sex, and race subgroups. The studies did not include any subjects younger than 19 years of age.

### 7.5.4 Drug-Disease Interactions

A review of adverse events by subpopulations categorized by concomitant diseases revealed no safety concerns.

### 7.5.5 Drug-Drug Interactions

No drug interaction studies have been conducted during the lifitegrast clinical development program.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

There have been no lifitegrast studies performed which suggest a tumorigenic potential.

## 7.6.2 Human Reproduction and Pregnancy Data

Pregnant women and nursing mothers were excluded from the clinical development program for lifitegrast. There have been no human reproduction or pregnancy studies performed.

Though pregnant and lactating females were excluded from participation in the all clinical studies and women of childbearing potential had to use adequate methods of birth control during the study, one subject reported pregnancy during the clinical development program. Subject 11-11250, a 41-year old female in the OPUS-1 study, was randomized to vehicle. On Day 86, she had a positive pregnancy test result. Her last menstrual period was on Day 51. Treatment with the investigational product was discontinued due to the pregnancy. The estimated date of delivery was December 2012. The outcome of the pregnancy was unknown. The subject was discontinued from the study on Day 86 due to the pregnancy. No further information was provided in the NDA submission.

## 7.6.3 Pediatrics and Assessment of Effects on Growth

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 PeRC on 5/14/15. PeRC concurred clinical studies in this population are impractical (see above).

## 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with lifitegrast. No reports of overdose were received during the clinical studies.

## 7.7 Additional Submissions / Safety Issues

The 4-Month Safety Update was submitted on June 3, 2015. Per the applicant:

Based on the review of safety data with masked treatment assignments from OPUS-3 as of a cut-off date of 20 Apr 2015, lifitegrast has been well tolerated. The majority of TEAEs observed were mild to moderate in severity and ocular in nature. No serious TEAEs have been reported in the study. The observed safety profile up to 20 Apr 2015 in OPUS-3 has demonstrated no changes in frequency, severity, or specificity of known events associated with lifitegrast and no pattern of AEs suggesting systemic toxicities, localized or systemic infections, or immunosuppressive complications. The OPUS-3 safety profile is similar to data from the previous Phase 3 studies, OPUS-1, OPUS-2, and SONATA.

## 8 Postmarket Experience

Lifitegrast is not a marketed drug product. There are no Postmarketing data to report.

APPEARS THIS WAY ON ORIGINAL

## **9 Appendices**

### **9.1 Literature Review/References**

*An independent literature review did not produce any additional significant information regarding lifitegrast.*

### **9.2 Advisory Committee Meeting**

*The application did not raise any issues which were thought to benefit from a discussion at an Advisory Committee meeting.*

### **9.3 Labeling Recommendations**

*A formal labeling review is deferred until additional data is submitted to support the proposed indication.*

## 9.4 Clinical Investigator Financial Disclosure

### Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 208-073

Submission Date(s): February 25, 2015

Applicant: Shire Development, LLC.

Product: Xiidra (lifitegrast ophthalmic solution) 5%

Reviewer: Rhea A. Lloyd, MD

Date of Review: March 3, 2015

Covered Clinical Studies (Name and/or Number):

1118-KCS-100, 1118-KCS-200, 1118-DRY-300 and 1118-DRY-400.

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: Study 1118-KCS-100: 5 investigators with 8 sub-investigators Study 1118-KCS-200: 13 investigators with no subinvestigators Study 1118-DRY-300: 31 investigators with no subinvestigators Study 1118-DRY-400: 22 investigators with no subinvestigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None.</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>None</u> Significant payments of other sorts: <u>None</u> Proprietary interest in the product tested held by investigator: <u>None</u> Significant equity interest held by investigator in sponsor of covered study: <u>None</u>		
Is an attachment provided with details of the disclosable financial	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>None</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.<sup>1</sup> Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

*Shire Development, LLC. has determined there were no financial interests or arrangements to disclose from investigators in studies 1118-KCS-100, 1118-KCS-200, 1118-DRY-300 and 1118-DRY-400 as indicated on Form FDA 3454.*

*Attachment 1 to Form FDA 3454 contains a table which details the disclosure of the financial interests for all investigators. The response entered is 'No' for all investigators in each study under the heading 'Financial Interest Disclosed?'. This table appears to contradict the applicant's response on Form FDA 3454. Clarification was requested from the applicant, who confirmed in an email dated March 10, 2015, that all investigators listed in Attachment 1 did not have any financial interests to disclose.*

*Shire Development, LLC. took the following steps to minimize potential bias of clinical study results by any of the investigators:*

- *Studies 1118-KCS-100, 1118-KCS-200, and 1118-DRY-300 included in this submission are double-blind randomized trials. The actual treatment given to individual subjects is determined by a randomization schedule. In no instance should an investigator treating patients in these trials have known the sequence of potential treatment assignments. Per protocol the randomization code in these trials was not to be broken except in emergency situations.*

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<sup>1</sup> See [web address].

- *All trial protocols were reviewed and approved by the Institutional Review Board (IRBs) before its initiation in order to ensure that financial interests of the trial investigators did not compromise the protection of research subjects.*
- *The clinical trials were monitored by an external Contract Research Organization according to the principles of Good Clinical Practice.*

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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.**  
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/s/  
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RHEA A LLOYD  
08/11/2015

WILLIAM M BOYD  
08/12/2015

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number:**

**208073**

**Applicant:**

**Shire Development, LLC**

**Stamp Date:**

**February 25, 2015**

**Drug Name:**

**Xiidra (lifitegrast ophthalmic solution) 5.0%**

**NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
<b>505(b)(2) Applications</b>					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSE</b>					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?  Study Number: 1118-KCS-100  Study Title: A Phase 2, Multicenter, Randomized, Double-	X			

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	masked and Placebo-controlled Study Evaluating the Efficacy of Three Different Concentrations (0.1%, 1.0%, 5.0%) of SAR 1118 Ophthalmic Solution in Subjects with Dry Eye Using the Controlled Adverse Environment (CAE) Model  Sample Size: 230 subjects                      Arms: 3  Location in submission: Module 5.3.5.1				
<b>EFFICACY</b>					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1: 1118-KCS-200 Indication: Treatment of dry eye  Pivotal Study #2: 1118-DRY-300 Indication: Treatment of dry eye	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Topical ophthalmic drug. More than 300 subjects exposed at the proposed dose.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant is requesting a Full Waiver of pediatric assessment as indicated in the iPSP submitted March 27, 2014.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			See Statistical filing review for details.
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report	X			

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

\_\_\_\_\_  
 Reviewing Medical Officer Date

\_\_\_\_\_  
 Clinical Team Leader Date

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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.**  
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/s/  
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RHEA A LLOYD  
03/19/2015

WILLIAM M BOYD  
03/19/2015