CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA:	**208-073**
Submission Date:	**25 February 2015**
Drug Product:	**lifitegrast ophthalmic solution, 5% w/v**
Trade Name:	**Xiidra®**
Proposed Indication:	**Treatment of signs and symptoms of dry eye disease**
Proposed Dosing Regimen:	**1 drop into each eye twice daily**
Sponsor:	**Shire Development LLC**
Submission Type:	**Original NDA submission (NME)**
OCP Reviewer:	**Gerlie Gieser, Ph.D.**
Team Leader:	**Philip M. Colangelo, Pharm.D., Ph.D.**

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I. Executive Summary

Lifitegrast is an antagonist of lymphocyte function-associated antigen-1 (LFA-1). The anti-inflammatory effect of lifitegrast is believed to be mediated by interfering with the binding of LFA-1 to its ligand, intercellular adhesion molecule-1 (ICAM-1), an interaction that is critical to the immune system function of lymphocytes and other leukocytes.

Lifitegrast (Xiidra®) ophthalmic solution 5% w/v was developed for the treatment of the signs and symptoms of dry eye disease (DED), a disease which may be associated with an underlying inflammatory condition. Three Phase 3 clinical trials were conducted by the sponsor; DRY-200 (OPUS-1) and DRY-300 (OPUS-2) evaluated efficacy and safety whereas DRY-400 (SONATA) was mainly a safety trial. SONATA and OPUS-2 used the proposed commercial product (Xiidra®) whereas OPUS-1 used a formulation with slightly different composition. The sponsor reported a paradoxical efficacy response in OPUS-1 and OPUS-2. Based on the sponsor's analysis, in OPUS-1 and OPUS-2, lifitegrast improved symptoms (eye dryness score or EDS) but not signs (corneal staining score reduction) of DED in patients with moderate to severe symptoms at baseline or EDS ≥40; in OPUS-1, lifitegrast reduced signs but did not improve symptoms of DED in patients with mild to moderate symptoms at baseline or EDS <40.

A. Recommendations

The Clinical Pharmacology information in this NDA is acceptable, provided that satisfactory agreement is reached

between the sponsor and the FDA regarding the language in Section 12 of the package insert. The PK characteristics of the final, to-be-marketed lifitegrast 5% ophthalmic solution (as evaluated in Phase 3 Study SONATA) should be included in the labeling; see Section III. Detailed Labeling Recommendations.

B. Phase IV Commitments
None.

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

Human Pharmacokinetics and Pharmacodynamics (Clinical Studies)
In Phase 1 Study 001, the plasma and tear fluid pharmacokinetics (PK) of lifitegrast were investigated following topical ocular (single dose, twice daily and thrice daily) administration of various strengths of a *prototype* lifitegrast formulation. 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 EC_{50} (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 sponsor 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.

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II. Question Based Review

A. General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Lifitegrast ophthalmic solution (formerly SAR 1118, SSP-005493, and SPD606; Figure 1) was originally developed by SARcode Bioscience, Inc. for the treatment of the signs and symptoms of dry eye disease (DED).

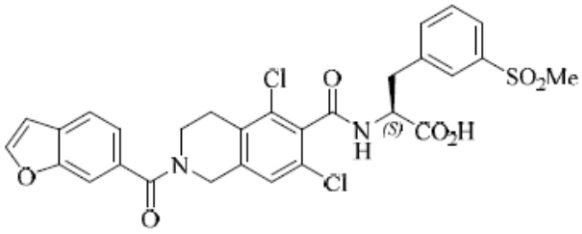

Figure 1. Lifitegrast; $C_{29}H_{24}C_{l2}N_2O_7S$; MW 615.48

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

The proposed commercial product ("Formulation #4") is a preservative-free, (b) (4) sterile eye drop containing 5% w/v of lifitegrast. The ophthalmic solution has a target pH of 7 to 8, and 200 -300 mOsm/kg. This product was evaluated for safety in Phase 3 Study SONATA and for efficacy in Phase 3 Study OPUS-2.

Note that a prototype product ("Formulation #1") was evaluated in the Phase 1 Study SAR 1118-001. In contrast to Formulation #4, Formulation #1 contains (b) (4) (b) (4)

See also Section II. E. General Biopharmaceutics.

3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The protein-protein interaction between lymphocyte function-associated antigen-1 (LFA-1) and its cognate ligand (intercellular adhesion molecule-1 or ICAM-1) is critical to the immune system function of lymphocytes/leukocytes. Lifitegrast binds to LFA-1 and prevents its interaction with ICAM-1, thus diminishing the recruitment of leukocytes to sites of inflammation and inhibiting the leukocyte component of inflammation and immune activation including lymphocyte adhesion, infiltration, proliferation, and cytokine release.

The proposed indication of lifitegrast ophthalmic solution (5%) is for the treatment of the signs and symptoms of dry eye disease (b) (4).

4. What are the proposed dosage(s) and route(s) of administration?

In the Phase 2 and all three Phase 3 trials, lifitegrast 5% ophthalmic solution was administered twice daily (BID) as a single drop in each eye.

In Phase 3 Study SONATA, contact lenses were reinserted 15 minutes after administration of lifitegrast. In the Phase 2 Study and in Phase 3 Studies OPUS-1 and OPUS-2, contact lens wear was avoided 7 days prior to and for the duration of the study.

B. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 summarizes the features of the clinical studies conducted to evaluate lifitegrast ophthalmic solution for the treatment of dry eye disease. Phase 1 Study SAR 1118-001 and Phase 3 Study 1118-DRY-400 (SONATA) evaluated the systemic exposures to lifitegrast following topical ocular administration of lifitegrast ophthalmic solutions. Specifically, in the Phase 1 trial, the PK profiles of lifitegrast in plasma and tears were determined in healthy subjects following 1 day and 10 days of topical ocular (BID or TID) administration of varying strengths of prototype lifitegrast ophthalmic solutions including 5% w/v. In the SONATA trial, lifitegrast plasma trough concentrations, as well as CD3, CD4, and CD8 lymphocyte counts, were measured on days 180 and 360 in dry eye disease patients treated with the proposed commercial ophthalmic formulation.

In the Phase 2 and all three Phase 3 trials, lifitegrast 5% ophthalmic solution was administered twice daily (BID) as a single drop in each eye.

Table 1. Clinical Studies Included the Lifitegrast Development Program

Study	Primary Study Objective	Study Design and Type of Control	Investigational Product: Dosage Regimen, Route of Administration	Number of Subjects Enrolled	Diagnosis (Population)	Duration of Treatment
SAR 1118-001 (Phase 1)	To assess safety and tolerability	Phase 1, randomized, double-masked, placebo-controlled, dose-escalation study	Lifitegrast 0.1, 0.3, 1.0, or 5.0% or placebo ophthalmic solution; Period 1: single dose, single drop Period 2: single drop BID Period 3: single drop TID	28	Healthy subjects	21 days of treatment separated by observation days (Period 1:1 day; Period 2:10 days; Period 3:10 days)
1118-KCS-100 (Phase 2 dry eye)	To evaluate efficacy as assessed by inferior corneal staining measured without use of the CAE at Day 84	Phase 2, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 0.1, 1.0, or 5.0% or placebo ophthalmic solution; single drop BID	230	Subjects with dry eye disease	84 days (12 weeks)
1118-KCS-200 (SPD606-301; OPUS-1)	To evaluate efficacy as assessed by change from baseline to Day 84 in inferior corneal fluorescein staining and VR-OSDI and to evaluate safety and tolerability	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	588	Subjects with dry eye disease	84 days (12 weeks)
1118-DRY-300 (SPD606-302; OPUS-2)	To evaluate efficacy as assessed by change from baseline to Day 84 in inferior corneal fluorescein staining score and eye dryness score, and to evaluate safety and tolerability	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	718	Subjects with dry eye disease with a history of artificial tear use within 30 days of screening	84 days (12 weeks)
1118-DRY-400 (SPD606-303; SONATA)	To evaluate safety as assessed by ocular and non-ocular adverse events	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID	332	Subjects with dry eye disease	360 days (1 year)

Adapted from NDA 208-073; Table 1 of synopses-indiv-studies.pdf

2. What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Phase 3 Study SONATA is a safety trial that evaluated both PK and PD endpoints in a subset of dry eye disease (DED) patients. Since lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist, the effect of repeated topical ocular administration of the proposed to-be-marketed lifitegrast ophthalmic solution on whole blood CD3, CD4, CD8 lymphocyte counts was determined in this trial.

For the Phase 3 clinical efficacy trials, the primary endpoint for DED *signs* was inferior corneal staining score (ICSS) for both OPUS-1 and OPUS-2 studies. For DED *symptoms*, the primary endpoints for OPUS-1 and OPUS-2 were visual-related function subscale of Ocular Surface Disease Index (VR-OSDI) and eye dryness score (EDS), respectively. See Table 2 for a complete listing of all key efficacy endpoints and key elements of these pivotal efficacy trials.

Table 2.
Summary of the Study Endpoints and other Key Elements of the Lifitegrast Clinical Efficacy Studies in Dry Eye Disease

	Phase 2	OPUS-1	OPUS-2
Sample size	230	588	718
Primary sign	ICSS	ICSS	ICSS
Primary symptom	None pre-specified	VR-OSDI score	EDS
Study arms	Placebo, 0.1%, 1.0%, 5.0% lifitegrast	Placebo, 5.0% lifitegrast	Placebo, 5.0% lifitegrast
Schedule	BID for 84 days	BID for 84 days	BID for 84 days
Key I/E	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in ≥1 eye • STT ≥1 and ≤ 10 • Change in ICSS ≥+ 1 pre-post CAE • ODS ≥+ 3 at 2 consecutive time points intra-CAE	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in any eye • STT ≥1 and ≤ 10 • Change in ICSS ≥+ 1 pre-post CAE • ODS ≥+ 3 at 2 consecutive time points intra-CAE	• Adults with DED • Cornea score of ≥2.0 in any eye • Redness score ≥1.0 in any eye • STT ≥1 and ≤ 10 • EDS ≥40 at screening and baseline • ICSS > 0.5 at screening and baseline • Recent AT use required
CAE	Yes	Yes	No
Rescue treatment allowed	No	No	No
Key sign measurements	• Corneal fluorescein score • Conjunctival lissamine score • STT	• Corneal fluorescein score • Conjunctival lissamine score • STT	• Corneal fluorescein score • Conjunctival lissamine score • STT
Key symptom measurements	• ODS • 7-item VAS • OSDI	• ODS • 7-item VAS • OSDI	• ODS • 7-item VAS • OSDI

AT=artificial tears; BID=twice daily; CAE=controlled adverse environment; EDS=eye dryness score; ICSS=inferior corneal staining score; I/E=inclusion/exclusion criteria; ODS=ocular discomfort score; OSDI=Ocular Surface Disease Index; STT=Schirmer Tear Test without anesthesia (mm/5min); VAS=visual analogue scale; VR-OSDI=visual-related function subscale of OSDI

Source: NDA 208073, clinical-overview.pdf

3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, refer to II.F. Analytical section.

4. Exposure-response

a) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for <u>efficacy</u>? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

<u>Note:</u> Plasma exposure-efficacy relationships were not explored because (1) the drug is administered directly to the site of action, and (2) any drug that is measured in systemic circulation is not considered relevant to the efficacy of the product for the treatment of dry eye disease syndrome. See also Section 5a of this NDA review.

Regarding the onset of pharmacological response, the sponsor reported that the onset of effects was 2 weeks after starting treatment with the proposed lifitegrast ophthalmic product 5%.

b) What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

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 (pre-treatment), 180 and 360. In the 9 patients with detectable (≥ 0.5 ng/mL) plasma lifitegrast trough concentrations (C_{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 over-immunosuppressive complications in 2 of the 9 patients with $C_{trough} \geq 2.5$ ng/mL, as well as in the additional patient with treatment-emergent PCI lymphocyte counts (i.e., CD8 < 220/mcL) measured on Day 180. Of the remaining 6 patients, 1 patient with a detectable C_{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_{50} needed to inhibit T cell adhesion (3.69 nM = 2.5 ng/mL) *in vitro*.

Table 3. Plasma lifitegrast trough (predose) concentrations in 9 patients with detectable concentrations on 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 [c]
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 [a]	175	0.555
1118_DRY_400-45-022	189	1.98
1118_DRY_400-45-025	185 358	3.31 [c] 1.17
1118_DRY_400-45-041 [b]	184	1.84

LLOQ of plasma PK assay = 0.5 ng/mL

[a] Patient 45-021 had consistently Potentially Clinically Important (PCI) abnormal CD8 counts < 220 µL, 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.

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

[c] lifitegrast trough concentrations above the EC_{50} needed for 50% inhibition of T cell adhesion (2.5 ng/mL) *in vitro*.

c) Does this drug prolong the QT or QTc interval?

In the Phase 1 trial, 12-lead Electrocardiograms (ECG's) were performed at screening, Day 0, Day 16, and Day 29 or early termination. Healthy subjects treated BID or TID for 10 days with up to 5% strengths of the prototype ophthalmic formulation did not have a clinically significant shift from baseline in ECG results; mean changes from baseline heart rate, PR interval, QT interval, Bazett-corrected QT interval, and QRS interval were similar between placebo and lifitegrast treatment groups. ECG's were not assessed in dry eye disease patients.

d) Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dosing regimen (1 drop twice daily) of lifitegrast ophthalmic solution 5% was evaluated in all three Phase 3 clinical trials involving dry eye disease patients.

5. What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

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 ± SD (range) plasma lifitegrast Cmax was 1.70 ± 1.36 (≤ 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 Cmax 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 ≥ 11.8 ng/mL and ≥ 164 ng/mL at 24-hour post-dose and 8-hour post-dose, respectively.

b) How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

In Phase 3 Study SONATA, the trough (pre-dose) concentrations of lifitegrast in plasma were determined at Days 0, 180, and 360 (Months 0, 6, and 12) in a subset of dry eye disease patients (n ≥ 43) treated with the proposed *commercial* ophthalmic product.

Nine patients (approximately 20%) had detectable (>0.5 ng/mL), plasma lifitegrast trough concentrations (C_{trough}) on days 180 and/or 360; values ranged from 0.55 to 3.74 ng/mL. Note that in the Phase 1 study where healthy subjects received the *prototype* 5% ophthalmic solution (1 drop BID for 10 days), all plasma samples collected after 30 minute post-dose (including pre-dose on day 10) were < 0.5 ng/mL. Sample size difference and the higher variability in the patient population vs. healthy subjects could have also contributed to the apparently higher pre-dose or trough concentrations of lifitegrast in the Phase 3 trial following topical ocular administration of lifitegrast 5% ophthalmic solution, i.e., detectable plasma lifitegrast C_{trough} in 9 of 47 DED patients versus in 0 of the 5 healthy subjects.

c) What are the characteristics of drug absorption?

In Phase 3 Study SONATA, repeated topical ocular administration of the proposed lifitegrast 5% ophthalmic solution 1 drop twice daily resulted in approximately 20% DED patients having detectable pre-dose or trough lifitegrast concentrations (≥ 0.5 ng/mL) in plasma but no apparent clinically significant chronic immunosuppression. See also Sections 4b, 5a, 5b above.

d) What are the characteristics of drug distribution?

Human plasma protein binding of lifitegrast was approximately 99%, independent of concentration (50 to 1000 ng/mL). Binding to isolated human serum albumin was 95% to 98%, and 31.6% to 51.1% to human α1-acid glycoprotein.

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

Following topical ocular administration, systemic concentrations of lifitegrast were low to not warrant conducting clinical pharmacology studies including a mass balance study. See also responses to Questions 5f and 5g below.

f) What are the characteristics of drug metabolism?

An *in vivo* drug metabolism study was not conducted in humans. Based on the findings of an *in vitro* metabolism study using fresh human hepatocytes, lifitegrast does not appear to undergo significant metabolism.

g) What are the characteristics of drug excretion?

Following topical ocular administration in healthy subjects, lifitegrast concentrations in the plasma were detectable only during the first 15 minutes post-dose; it was not possible to calculate plasma elimination half-life and other clearance related PK parameters of lifitegrast.

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Since plasma lifitegrast concentrations were only detectable in healthy subjects who received the two highest strengths (1% and 5%) of the *prototype* lifitegrast formulation, it is not possible to assess linearity or non-linearity of dose-concentration relationship. The mean and median lifitegrast Cmax after topical ocular BID dosing of lifitegrast ophthalmic solution were numerically higher after dosing with 5% solution than with 1% solution.

i) How do the PK parameters change with time following chronic dosing?

In the Phase 1 trial that investigated the single dose and repeat dose PK of the *prototype* formulation of lifitegrast ophthalmic solution 5% given 1 drop twice daily (BID), both the mean plasma Cmax and AUC on Day 10 were approximately 3.5-fold higher than those measured on Day 1 of BID dosing.

j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

As would be expected for products administered via the topical ocular route, the inter-subject variability of systemic drug exposures was high. In the Phase 1 trial (healthy subjects), the coefficient of variations about the mean lifitegrast Cmax were approximately 225% and 80% for the 1% and 5% strengths of the prototype ophthalmic formulation, respectively. In the Phase 3 trial SONATA (dry eye disease patients), the coefficient of variation about the mean lifitegrast C_{trough} was approximately 265% to 465% for the proposed lifitegrast solution 5%.

C. Intrinsic Factors

1. **What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?**

   None. In Phase 3 Study SONATA, the small number of patients that had detectable and highly variable plasma concentrations did not warrant a meaningful formal subgroup analysis of PK, and exploration of exposure-systemic safety relationships. Only one dosing regimen (1 drop twice daily) of the to-be-marketed ophthalmic 5% product was evaluated for safety in SONATA, and for efficacy/safety in Phase 3 Study OPUS-2.

   Based on the sponsor's analysis of efficacy data in Phase 3 Study OPUS-2, there were no apparent age-, gender-, and race-dependent differences in response (in terms of signs and symptoms) to the proposed to-be-marketed lifitegrast 5% ophthalmic solution. Note that in Phase 3 Study OPUS-2, all DED patients had baseline (disease severity) Eye Dryness Score ≥ 40.

2. **Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments**

are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

There are no dosage adjustment recommendations based on exposure-systemic safety relationship considerations in population subgroups. Furthermore, based on the sponsor's pooled analysis, the safety profile was consistent across age, gender and race subgroups; see below for additional information.

a) elderly

Based on the sponsor's analysis of the data from Phase 3 Study SONATA, the frequencies of non-ocular treatment-emergent adverse events (TEAEs) were similar between patients ≥ 65 years and < 65 years. Per the sponsor's proposed labeling, at least a third of the patients were elderly (≥ 65 years old) and no differences in non-ocular, as well as ocular, safety and efficacy was observed versus younger patients.

b) pediatric patients

The sponsor requested a full waiver of research on pediatric patients 0-17 years old since the necessary studies are impossible and highly impracticable to conduct (e.g., as evidenced by the little to no scientific epidemiologic evidence of DED in the pediatric study population). On 22 July 2014, the FDA agreed with the sponsor's Initial Pediatric Study Plan (iPSP). The sponsor's proposed package insert states that the safety and efficacy of the proposed lifitegrast ophthalmic product in children had not been established.

c) gender

Majority of the patients enrolled in the clinical trials were female (75-80%) and Caucasian (85-94%), reflective of the total dry eye disease population. In the sponsor's pooled analysis, a higher frequency of non-ocular TEAEs (e.g., dysgeusia) in females vs males was reported, (e.g., in the Phase 3 SONATA trial, in both placebo [41% vs 19%] and lifitegrast 5% [53% vs 29%] treatment groups).

d) race

There were not adequate non-Caucasian patients enrolled in the trials to warrant a meaningful racial subgroup analysis.

e) renal impairment

A dedicated PK study in patients with varying degrees of renal impairment was not conducted and was not deemed necessary due to the apparently limited extent of systemic absorption of lifitegrast following topical ocular administration, and considering the apparently low contribution of urinary excretion to the overall elimination of intravenous and topical ocular lifitegrast in animals.

f) hepatic impairment

A dedicated PK study in patients with varying degrees of hepatic impairment was not conducted and was not deemed necessary due to the apparently limited extent of systemic absorption of lifitegrast following topical ocular administration, and the apparently limited contribution of hepatic metabolism to lifitegrast elimination using human hepatocytes.

g) what pharmacogenetics information is there in the application and is it important or not

None.

h) what pregnancy and lactation use information is there in the application?

The sponsor reported that in rats and rabbits, lifitegrast was not teratogenic when administered up to 30mg/kg/day via intravenous injection.

i) other human factors that are important to understanding the drug's efficacy and safety

None.

D. Extrinsic Factors

1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

Due to the limited and highly variable systemic absorption of lifitegrast following topical ocular administration of the proposed lifitegrast 5% ophthalmic solution, the influence of concomitant medications and other extrinsic factors on systemic safety of DED patients who participated in Phase 3 SONATA was not explored.

Note that in Phase 3 Study OPUS-2, all DED patients had prior history of artificial tear substitute use within 30 days prior to Study Visit 1.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None. Due to the lack of relevance of plasma lifitegrast concentrations on the efficacy of the proposed ophthalmic product, and the limited and highly variable systemic absorption of lifitegrast following topical ocular administration, dosage adjustment recommendations for lifitegrast 5% ophthalmic solution based on the influence of these extrinsic factors on plasma lifitegrast concentrations were not provided, nor are they warranted.

3. Drug-Drug Interactions

Dedicated clinical drug-drug interaction studies were not conducted for lifitegrast ophthalmic solution 5%. Safety analysis based on concomitant use of systemically administered medications was not performed.

a) is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?
None.

b) is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?
No *in vitro* and *in vivo* studies were conducted to investigate the CYP450 substrate status of lifitegrast because of the observed minimal metabolism of lifitegrast in an *in vitro* human hepatocyte system.

Following incubation of radiolabeled lifitegrast (10 mcg/mL) with primary isolated fresh human hepatocytes for 4 hours, radioactivity decreased by 8.5% and by 5.2% for the 10 mcg/mL sample versus the control incubations, respectively. Per the sponsor, the study was not able to reliably distinguish the true metabolites from the degradation products of lifitegrast, and was not able to elucidate the structure of the putative metabolite (with molecular mass higher than lifitegrast).

c) is the drug an inhibitor and/or an inducer of CYP enzymes?

The potential of topical ocular lifitegrast to inhibit the activities of CYP2C9 and CYP3A4 is remote; further *in vitro* studies to investigate inhibition/induction of CYP450 enzymes are not indicated.

The sponsor conducted an *in vitro* study using a human liver microsomal system to investigate the CYP2C9 and CYP3A inhibitory potential of lifitegrast for the following reasons: (1) In a fluorescent screening assay against a panel of more than 105 potential biological targets, lifitegrast (10 µM) was found to inhibit CYP2C9 by 94%. (2) The main clearance of topical ocular lifitegrast is believed to occur via the nasal and subsequently gastrointestinal tract, so it was hypothesized that gut CYP3A4 could potentially be affected. Based on the findings of the *in vitro* human liver microsomal study, lifitegrast inhibited CYP2C9 with an IC_{50} of 4.1 µM, and CYP3A4-mediated metabolism of midazolam and testosterone with an IC_{50} of 42 µM and 32 µM, respectively. Based on the follow-on study, the K_I (unbound inhibition constant) for CYP3A4 with midazolam as the substrate is 107 µM. Given that the mean plasma lifitegrast Cmax after 10 days dosing of the *prototype* formulation (1 drop twice daily) to healthy subjects is 1.7 ng/mL (< 3 nM), the reviewer considers a remote potential for systemically absorbed lifitegrast (following topical ocular administration of the proposed product) to inhibit *in vivo* metabolism of drugs that are substrates of CYP2C9 and/or CYP3A. (Note that based on the evaluation of a

basic model parameter (R_2) as suggested in the 2012 draft FDA Drug-Drug Interaction Guidance, the sponsor concluded that lifitegrast has potential for time-dependent *in vivo* inhibition of intestinal CYP3A. However, the reviewer does not consider this particular finding to be of meaningful relevance to topical ocular lifitegrast.)

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?
No. Based on the sponsor's *in vitro* studies with absorption/efflux transporters, lifitegrast (5, 30 and 100 µM) was not shown to be a substrate of P-glycoprotein and breast cancer resistance protein (BCRP), using the human MDCK monolayer system.

e) are there other metabolic/transporter pathways that may be important?
Based on the findings of an *in vitro* study using CHO, MDCKII or HEK293 cell lines expressing the respective uptake transporters, the sponsor concluded that lifitegrast (2 and 20 µM) is a substrate of OATP1A2 and OATP2B1 transporter but not OATP2A1. The clinical relevance of these *in vitro* findings is rather limited given that the lifitegrast Cmax is < 3 nM following repeated topical ocular administration of the prototype lifitegrast 5% ophthalmic solution to healthy subjects.

Lifitegrast was not shown to be a substrate of BCRP; see 3d above.

f) does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?
No.

g) what other co-medications are likely to be administered to the target patient population?
Not applicable

h) are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?
None.

i) is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?
None.

j) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?
None.

k) **What issues related to dose, dosing regimens or administration are unresolved, and represent significant omissions?**
None.

E. General Biopharmaceutics

Table 4 provides a comparison of the chemical composition of the *prototype* Formulation #1 used in the Phase 1 trial and the proposed *commercial* Formulation #4 used in Phase 3 Studies SONATA and OPUS-2. No *in vivo* animal or human study was conducted for a head-to-head comparison of the *prototype* (Formulation #1) versus the proposed *commercial* (Formulation #4) lifitegrast ophthalmic solution, in terms of ocular PK and/or plasma PK of lifitegrast.

Table 4.
Chemical composition of various lifitegrast 5% ophthalmic formulations and history of usage in the clinical program

	Formulation Number			
	1	2	3	4
Clinical Usage	**SAR 1118-001** Phase 1	1118-KCS-100 Phase 2 **Study 1**	1118-KCS-200 Phase 3 **Study 2**	111-DRY-400 Phase 3 **Safety**
Container System	(b) (4) Container/LDPE Dropper Tip	LDPE (b) (4) Foil pouch		
Component	**Quantity (mg/mL)**			
SAR 1118	50.0	50.0	50.0	50.0
(b) (4)	(b) (4)			
Sodium thiosulfate, pentahydrate				
(b) (4)				
Sodium phosphate, dibasic, anhydrous				
(b) (4)				
Sodium chloride				
(b) (4)				
Sodium hydroxide				
Hydrochloric acid				
Water for Injection				
(b) (4)				

qs: quantum sufficit
N/A: Not applicable; not used in formulation or process
Formulation 4 is the *proposed to-be-marketed* formulation and was evaluated in Phase 3 Studies 111-DRY-300 (OPUS-2) and 111-DRY-400 (SONATA).
Source: Clinical Pharmacology review of IND 77,885, SDN-32

F. Analytical Section

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What are the performance characteristics of the PK assay? What is the sample stability under the conditions used in the study?

For the plasma samples from the Phase 1 and Phase 3 trials, a validated LC/MS/MS method was used to determine lifitegrast concentrations in human K3 EDTA plasma. The sponsor reported that all PK assay runs met the predefined acceptance criteria.

The linear concentration range was 0.500 to 100 ng/mL; the lower limit of quantitation (LLOQ) was 0.500 ng/mL. The LLOQ (0.5 ng/mL) in plasma is acceptable as it is below the EC_{50} (4 nM ~2.5 ng/mL) for LFAT-1 antagonism *in vitro*, as well as the EC_{50} (2 nM ~1.2 ng/mL) for inhibition of IL_2 (pro-inflammatory cytokine) release.

The overall inter-run accuracy (%RE) and inter-run precision (%RSD) for the QC samples at three concentrations (1.50, 5.00, and 80.0 ng/mL) of lifitegrast over the three batch runs was ≤ 4.13% (absolute), and ≤ 3.14%, respectively. In each of three batch runs, six replicates of QC samples at three concentrations (1.50, 5.00, and 80.0 ng/mL) were analyzed. The intra-run precision in these runs was ≤ 3.19% and the accuracy was ≤ 7.50% (absolute) for lifitegrast. An overall mean extraction recovery of 95.7% was observed for lifitegrast; 95.2% for the internal standard. No significant interfering peaks (>20% of the lower limit of quantitation or of the mean internal standard response) due to endogenous compounds or reagents were observed at the retention time of lifitegrast and the internal standard (SAR1118-d6)

Lifitegrast is stable in human K3 EDTA plasma for at least 25.5 hours at benchtop conditions, for at least 4 days at –70°C, and for at least four freeze (-70°C) and thaw (room temperature) cycles before processing. Lifitegrast is stable in processed human plasma for at least 71 hours at room temperature.

For the tear fluid samples from the Phase 1 trial, a validated LC/MS/MS method was used to determine lifitegrast concentrations in human tear; 0.8 sodium chloride solution was used as proxy matrix in assay validation studies.

The linear range in tears was 5.00 to 1000 ng/mL; the lower limit of quantitation (LLOQ) was 5.00 ng/mL, and samples with an analyte concentration higher than 1000 ng/mL can be diluted 10-fold successfully without compromising accuracy and precision. Inter-run precision and accuracy were determined by analyzing three concentrations (15.0, 150, and 800 ng/mL) of QC samples in replicates of six over three separate batch runs. The overall precision and accuracy for the QC samples at three concentrations of lifitegrast over the three batch runs were ≤ 6.82% and ≤ 7.33%, respectively. In each of the three batch runs, six replicates of QC samples at three concentrations (15.0, 150, and 800 ng/mL) were analyzed. The intra-run precision and accuracy in these runs were ≤ 6.69% and ≤ 8.67%, respectively, for lifitegrast. An overall mean extraction recovery of 94.6% was observed for lifitegrast; 99.2% for the internal standard.

Lifitegrast is stable in 0.8% sodium chloride spiked Tear Flow Test Strips for at least 17 hours at benchtop conditions, and for at least three freeze (-20°C) and thaw (room temperature) cycles before processing. Lifitegrast in extracted (processed) sample is stable for at least 66 hours at room temperature, and for 333 hours at approximately 4°C prior to analysis.

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

B. Individual Study Reviews

1. Study SAR 1118-001

Title: A Phase 1, Randomized, Double-masked, and Placebo-controlled Dose Escalation Trial of the Safety and Tolerability of Single and Multiple Doses of SAR 1118 Ophthalmic Solution in Healthy Human Subjects

Name of Investigational Product: Lifitegrast ophthalmic solution (SAR 1118)
Development Phase of Study: Phase 1
Date of Study Initiation to Completion (last subject's last follow-up): 23 Aug 2008 to 06 Dec 2008

Relevant Publication: Semba CP, Swearingen D, Smith VL, Newman MS, O'Neill CA, Burnier JP, et al. 2011. Safety and pharmacokinetics of a novel lymphocyte function-associated antigen-1 antagonist ophthalmic solution (SAR 1118) in healthy adults. *J Ocul Pharmacol Ther*; 27(1): 99-104

Objectives:
-The primary objective of the study was to assess the safety and tolerability of single and multiple doses of 4 escalating concentrations of lifitegrast ophthalmic solution compared to placebo solution in healthy human subjects.

-The secondary objective of the study was to determine the pharmacokinetic profile in plasma and tears of single and multiple doses of 4 escalating concentrations of lifitegrast.

Methodology:
This was a randomized, double-masked, placebo-controlled, dose-escalation study conducted [at a single US center] 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, 1.0, and 5.0%)** of lifitegrast. The 7 subjects in each cohort were randomly assigned in a 5:2 ratio to receive either lifitegrast or placebo.

Screening procedures were completed within 21 days prior to Day 0. Subjects who completed screening assessments and were determined to be eligible completed Period 1 dosing (single dose), Period 2 dosing (twice daily for 10 days), Period 3 dosing (3 times daily for 10 days), and a 2-week follow-up period.

Dose (concentration) escalation and treatment of the next higher dose cohort only occurred after 6 of the 7 subjects in the prior dose cohort completed Period 1 and 10 days of treatment in Period 2. Dose escalation occurred only in the absence of severe systemic and ocular toxicity/adverse events (AEs), and if 6 of the 7 subjects in the prior cohort experienced no clinically significant adverse changes on ophthalmologic examination. A cohort review committee consisting of the principal investigator and the sponsor's medical monitor reviewed all AEs at the completion of 10 days of treatment in Period 2 for each cohort and determined whether escalation to the next dose level could occur.

Number of Subjects (Planned and Analyzed):
A total of 28 subjects were enrolled in the study and assigned to 1 of 4 cohorts that corresponded to the 4 escalating dose cohorts of lifitegrast or placebo. Within each cohort, 5 subjects were randomized to receive lifitegrast and 2 subjects were randomized to receive placebo. All subjects who enrolled completed the study.

Diagnosis and Main Criteria for Inclusion:
- Healthy male or female subjects, aged 18-50 years
- Current non-smoker
- Best corrected visual acuity (4 meters, Early Treatment Diabetic Retinopathy Study) at least 20/40 in each eye
- Body mass index between 19.9 and 29.9 kg/m^2
- No history of excessive alcohol use (as judged by the investigator) or illicit drug use/abuse
- No consumption of any alcohol or any illicit drugs within 1 week of first investigational product administration
- No use of any tobacco or nicotine-containing products within 6 months prior to first investigational product administration

- No blood donation or significant loss of blood within 56 days of Day 0
- No known history of dry eye, allergic conjunctivitis, iritis/uveitis, glaucoma, blepharitis, or other chronic ophthalmologic disorder
- No ocular symptoms/complaints within 1 month prior to Day 0
- No history of laser-assisted in situ keratomileusis or similar type of corneal refractive surgery within 12 months prior to Day 0, and/or any other ocular surgical procedure within 3 months prior to Day 0
- Does not require contact lenses; has not used contact lenses at any time within 1 month prior to Day 0
- No use of any prescription or over-the-counter medication or herbal products within 2 weeks or 5 half-lives (whichever was longer) of Day 0
- Had not taken any of the following medications/preparations within 1 month prior to Day 0: any ophthalmic preparation; any anticholinergic agent; any oral or nasal steroid

Investigational Product, Dose, Mode of Administration, and Lot/Batch Number(s):
Subjects received single and multiple daily doses of either lifitegrast (0.1, 0.3, 1.0, or 5.0%) or placebo ophthalmic solution administered to the ocular surface as an eye drop. The batch numbers for 0.1, 0.3, 1.0, and 5.0% lifitegrast were PLI-026-08, PLI-027-08, PLI 028-08, and PLI-029-08, respectively. The batch number for placebo was PLI-025-08.

Reviewer's comment:
Note that the formulation of the 5% ophthalmic solution used in this Phase 1 study is compositionally different from that used in the pivotal Phase 3 trials and to-be-marketed product.

Duration of Treatment:
Screening: Within 21 days of Day 0
Period 1: One dose (one eye) on Day 1
Period 2: Twice daily dosing (on each eye) for 10 days (Days 5-14)
Period 3: 3 times daily dosing (on each eye) for 10 days (Days 18-27)
Follow-up: 2 weeks (visits on Days 34 and 41)

Reviewer's comment(s):
The drop volume administered was 35 mcL. BID and TID dosing was approximately every 10-12 hours and every 6-8 hours, respectively. The ophthalmic solutions were taken out of the refrigerator and kept at ambient (room) temperature for at least 1 hour prior to administration. All study personnel were masked to treatment assignments.

Criteria for Evaluation:
Pharmacokinetics were assessed by serial tear and blood samples.

Plasma pharmacokinetic samples were obtained pre-dose, at 5 and 30 minutes post-dose and at 1, 4, 8, 24, and 48 hours post-dose on Days 1, 14, and 27. Plasma samples were obtained for pharmacokinetics pre-dose, at 5 and 30 minutes post-dose and at 1, 4, 8 (prior to PM/last dose), and 24 hours post-dose on Days 5 and 18. A single plasma sample was obtained for pharmacokinetics at Follow-up Week 1. The validated LC/MS/MS assay was linear over the range 0.500-100ng/mL with a LLOQ of 0.500ng/mL.

Tear pharmacokinetic samples were obtained from each eye (using Schirmer strips) pre-dose, at 30 minutes post dose and at 1, 4, 8, 24, and 48 hours post-investigational product administration on Day 1. Tear pharmacokinetic samples were obtained from 1 eye only (using Schirmer strips) pre-dose, at 30 minutes and at 1, 4, 8 (prior to PM last dose), and 24 hours post-dose (Days 5, 14, 18, and 27), and additionally at 48 hours post-dose (Days 14 and 27). A single tear pharmacokinetic sample was obtained (using Schirmer strips) from 1 eye at Follow-up Week 1. The validated LC/MS/MS assay was linear over the range 5 - 1000ng/mL with a LLOQ of 5 ng/mL.

Safety was assessed by:
- Adverse events
- Clinical laboratory evaluations (chemistry, hematology, and urinalysis)
- Vital signs (temperature, blood pressure, heart rate, respiration rate, and weight): at screening, Day 0, and at the end of each period (Days 4, 16, 29, and 41) or early termination

- Electrocardiograms (12-lead ECG's were obtained at screening, Day 0 (Period 1), Day 16 (Period 2), and Day 29 EOT (Period 3)
- Physical examination
- Ophthalmic examination (slit lamp biomicroscopy, corneal fluorescein staining, intraocular pressure [IOP], Schirmer Tear Test [STT], tear film break-up time [TFBUT], best corrected visual acuity [BCVA]).

Statistical Methods:
The Safety Population included all subjects who received at least 1 dose of investigational product.
The sample size chosen was generally accepted for Phase 1 studies of healthy human subjects. A total of 7 subjects per cohort, 5 receiving lifitegrast and 2 receiving placebo, permitted an adequate initial assessment of the safety and tolerability of lifitegrast. In Period 1, initial tolerability was assessed by administration of lifitegrast in 1 eye and placebo in the opposite eye in the same subject (for subjects assigned to lifitegrast). The placebo group, consisting of 8 subjects total (2 per lifitegrast dose cohort), provided a reasonable comparator group to assess adverse effects in this study population.

The primary endpoint was to measure safety and tolerability as assessed by physical examinations, electrocardiograms, vital signs, clinical laboratory measurements, and AEs to measure the systemic effects of lifitegrast and slit lamp biomicroscopy, IOP, STT, TFBUT, and BCVA to measure the local effects of lifitegrast.

Descriptive statistics were used to summarize the study results. Summary statistics, including mean, median, standard deviation, and range, were provided for continuous variables. Categorical variables were summarized by frequency and percentage.

Results:
Baseline demographic characteristics were similar between treatment groups. Subjects' age ranged from 19-47 years, with the mean (standard deviation) being 30.5 years (8.9). Over half of subjects (57%) were 18-29 years of age. All subjects were male, and the majority of subjects were Hispanic (89%). The mean (standard deviation) body mass index was 25.6kg/m^2 (2.3).

ISR Table 1. Demographic data (Safety Population)

	Lifitegrast				Placebo N=8 n (%)	Total N=28 n (%)
	0.1% N=5 n (%)	0.3% N=5 n (%)	1.0% N=5 n (%)	5.0% N=5 n (%)		
Age (years)						
Mean (SD)	24.4 (1.8)	37.2 (8.2)	38.8 (9.2)	27.6 (7.8)	26.9 (7.2)	30.5 (8.9)
Age group (n [%])						
18-29 years	5 (100)	1 (20)	1 (20)	4 (80)	5 (63)	16 (57)
30-39 years	0	2 (40)	1 (20)	0	2 (25)	5 (18)
40-50 years	0	2 (40)	3 (60)	1 (20)	1 (13)	7 (25)
Sex (n [%])						
Male	5 (100)	5 (100)	5 (100)	5 (100)	8 (100)	28 (100)
Female	0	0	0	0	0	0
Race (n [%])						
Caucasian	0	2 (40)	0	1 (20)	0	3 (11)
Hispanic	5 (100)	3 (60)	5 (100)	4 (80)	8 (100)	25 (89)
BMI (kg/m^2)						
Mean (SD)	23.7 (1.6)	27.2 (1.5)	26.9 (1.2)	25.3 (3.1)	25.1 (2.5)	25.6 (2.3)

BMI=body mass index; SD=standard deviation
Source: Table 4 of CSR

Pharmacokinetic Results:

Plasma Pharmacokinetic Summary:

Lifitegrast dose strengths of 0.1, 0.3, 1.0, and 5.0% 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 (1.0 and 5.0% lifitegrast), and the highest mean maximum concentration (Cmax) of lifitegrast in plasma was 1.70 ± 1.36ng/mL occurring on the last day of the lifitegrast 5.0% twice daily regimen. The lifitegrast plasma concentrations appeared early, with mean time of maximum observed concentration sampled during a dosing interval (tmax) 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.

ISR Table 2. Summary of Lifitegrast Plasma Pharmacokinetic Parameters in Healthy Subjects Receiving Single and Multiple Dose Regimens of Lifitegrast (Pharmacokinetic Population)

	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-8} (ng·h/mL)	AUC_{0-4} (ng·h/mL)
1.0% lifitegrast						
Period 2, Day 10	5[a]	0.18 ± 0.40	0.08	NC	0.04 ± 0.10	NC
Period 3, Day 10	5[b]	0.27 ± 0.37	0.09 ± 0.01	NC	NC	0.07 ± 0.10
5.0% lifitegrast						
Period 1, Day 1	5[c]	0.65 ± 0.68	0.22 ± 0.24	0.35 ± 0.48	NC	NC
Period 2, Day 1	5[c]	0.50 ± 0.49	0.22 ± 0.24	NC	0.20 ± 0.22	NC
Period 2, Day 10	5[d]	1.70 ± 1.36	0.09 ± 0.01	NC	0.69 ± 0.47	NC
Period 3, Day 1	5[d]	1.31 ± 1.04	0.19 ± 0.17	NC	NC	0.56 ± 0.48
Period 3, Day 10	5[d]	0.95 ± 0.60	0.08 ± 0.00	NC	NC	0.64 ± 0.65

[a] N=1 for t_{max}

[b] N=2 for t_{max}

[c] N=3 for t_{max}

[d] N=4 for t_{max}

Note: AUC_{0-t} is reported for Period 1 (single dose), AUC_{0-8} is reported for Period 2 (twice daily), and AUC_{0-4} is reported for Period 3 (3 times daily).

AUC_{0-4}=area under the curve from the time of dosing to 4 hours; AUC_{0-8}=area under the curve from the time of dosing to 8 hours; AUC_{0-t}=area under the curve from the time of dosing to the last measurable concentration; C_{max}=maximum concentration occurring at t_{max}; NC=not calculated; t_{max}=time of maximum observed concentration sampled during a dosing interval

Source: Section 14, Table 2.1.4

Source: Table 6 of CSR

Reviewer's comments:

-Lifitegrast was detected in plasma of patients assigned to the higher dose strengths (1% and 5%) of the ophthalmic solution.

For the 5% solution given BID to each eye:

-The maximum plasma lifitegrast concentration (3.71 ng/mL) was measured within 15 post-instillation (i.e., at 5 minutes post-dose) on Day 10 in a 19-year old male healthy subject treated with 5% lifitegrast 1 drop in each eye for 10 days. Lifitegrast was not detectable in plasma starting at 1 hour post-instillation, i.e., the Ctrough concentrations in the 5 healthy subjects were <LLOQ (< 0.5 ng/mL).

-The average plasma Cmax on Day 10 of BID (bilateral ocular) dosing was approximately 3.5-fold higher than on Day 1 of topical ocular lifitegrast 5% .

-Per the sponsor: Instead of AUC_{0-12h} , AUC_{0-8h} was presented because BID dosing was every 10 – 12 hours. However, the reviewer prefers not to report AUC_{0-8h} in the labeling because it appears that none of the plasma samples taken after 1 hour post-dose had concentrations above the LLOQ of the assay.

-BLLOQ concentrations were reported as "0" in the datasets, and treated as "0" in the PK parameter calculations.

**Compare to the pre-dose data at Months 6 and 12 in 9 (of 47; ~20%) DED patients with detectable lifitegrast concentrations in the SONATA trial: mean ± sd (range); median: 1.65 ± 1.09(0.555 – 3.74); 1.24 ng/mL.*

-The PK parameter values reported by the sponsor are otherwise generally consistent with the reviewer's confirmatory analysis.
-All PK assay runs met the predefined acceptance criteria. The LLOQ in plasma (0.5 ng/mL) is below the EC_{50} (2.5 ng/mL) for inhibition of T cell adhesion.
-The sponsor reported protocol deviations. The most notable incidents were related to apparent contamination of predose and placebo samples, which potentially undermines the accuracy of the tear fluid PK results. Such deviations were considered during the reviewer's confirmatory PK analysis. Two relevant examples for Period 2 (lifitegrast 5% BID) of the study are provided below.
Plasma:
-Day 10 predose concentration of Subject 04006 (taken postdose instead). Reviewer notes that in the pc.xpt and adpc.xpt, datasets, the predose value in question was already set to PCSTRESN="0"ng/mL.
-Storage temperatures (-80 ºC) for some plasma samples (not clear if for Period 2) were outside allowable limits ±15ºC on multiple days. Reviewer note: The greatest deviation was -30 ºC.

Tear:
-SUBJID ~~02002-73~~ 37-2002: tear sample weight = 0 mg since post-weight = preweight of Schirmer paper strip (Reviewer note: PLACEBO patient, thus no impact on PK analysis).

Table 2: Summary of Lifitegrast Tear Pharmacokinetic Parameters in Healthy Subjects Receiving Single and Multiple Dose Regimens of Lifitegrast (Pharmacokinetic Population)

Treatment	N	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-8} (ng·h/mL)	AUC_{0-4} (ng·h/mL)
Lifitegrast 5.0%						
Period 2, Day 1	5	48681 ± 56903	0.34 ± 0.01	NC	75493 ± 99762	NC
Period 2, Day 10	5	91413 ± 43308	0.44 ± 0.22	NC	127697 ±	NC

Reviewer's comment:
The median Tmax was 0.33 h for both days 1 and 10.

Tear Pharmacokinetic Summary:
The lifitegrast tear concentrations increased in a roughly dose-proportional manner over the 0.1-5.0% 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 Cmax and from 78.4-109.8% for tear area under the curve from the time of dosing to the last measurable concentration (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 unexpected accumulation* of lifitegrast in tears during the twice daily and 3 times daily regimens.

Safety Results:
Lifitegrast was generally well tolerated. The observed safety profile demonstrated no pattern of AEs suggesting systemic toxicities or localized infectious complications due to chronic immunosuppression.

A higher percentage of subjects in the 0.1% and 0.3% lifitegrast groups had treatment-emergent AEs (TEAEs) (60% and 100%, respectively) than the 1.0% lifitegrast and 5.0% lifitegrast, and placebo groups (20, 40, and 21%, respectively). A higher percentage of subjects with TEAEs was observed during Period 2 (twice daily dosing; 36%) than Period 1 (single dose; 11%) and Period 3 (3 times daily dosing; 29%).

The 0.3% lifitegrast group had a higher percentage of subjects with ocular TEAEs (100%) than the other treatment groups (18-20%). Although a higher percentage of subjects had ocular TEAEs in Period 2 (twice daily dosing; 21%) than Period 1 (single dose; 11%), a similar percentage of subjects had TEAEs in Periods 2 and 3 (twice [21%] and 3 times [18%] daily dosing, respectively). Similar percentages of subjects had ocular and non-ocular TEAEs (39% total for both).

The most common ocular TEAEs overall were eye irritation, eye pain, eye pruritus, eyelid pain, and ocular hyperemia. The most common non-ocular TEAEs overall were headache, erythema, and insomnia.

Summary of Most Common (Occurring in ≥2 Subjects) Treatment-emergent Adverse Events (Safety Population)

	Lifitegrast				Placebo N=28[a] n (%)	Total N=28 n (%)
	0.1% N=5 n (%)	0.3% N=5 n (%)	1.0% N=5 n (%)	5.0% N=5 n (%)		
Ocular						
Eye irritation	0	3 (60)	0	0	1 (4)	3 (11)
Eye pain	0	0	0	0	2 (7)	2 (7)
Eye pruritus	1 (20)	0	0	1 (20)	0	2 (7)
Eyelid pain	0	1 (20)	1 (20)	0	1 (4)	2 (7)
Ocular hyperaemia	0	1 (20)	0	1 (20)	1 (4)	2 (7)
Non-ocular						
Headache	0	3 (60)	0	0	1 (13)	4 (14)
Erythema	0	1 (20)	0	0	1 (13)	2 (7)
Insomnia	0	0	0	0	2 (25)	2 (7)

[a] N=8 for non-ocular TEAEs. In Period 1, non-ocular TEAEs were summarized under the active treatment group when active treatment was given in 1 eye. In Period 1, all 28 subjects received placebo in 1 eye.

All ocular TEAEs were mild to moderate in severity, and all non-ocular TEAEs were mild in severity. Most ocular TEAEs and the non-ocular TEAEs of dysgeusia and headache were considered possibly related to the investigational product by the investigator. All other non-ocular TEAEs were considered not related to the investigational product by the investigator. No subject experienced TEAEs that led to withdrawal, serious TEAEs, or TEAEs that led to death.

No clinically relevant trends were observed in clinical laboratory results (chemistry, hematology, or urinalysis), vital sign results, or 12-lead electrocardiogram results. The changes from baseline in the other ocular safety parameters (BCVA, STT, TFBUT, slit lamp biomicroscopy, and IOP) were minimal and similar between treatment groups.

Conclusions:

- Lifitegrast was generally well tolerated.
- Limited plasma exposure to lifitegrast was observed when administered by topical ocular instillation to healthy subjects up to 3 times daily in dose strengths of 0.1, 0.3, 1.0, and 5.0%.
- Lifitegrast tear Cmax typically occurred around 30 minutes after administration, and the lifitegrast tear Cmax and AUC increased in a roughly dose-proportional manner over the 0.1-5.0% dose range. There were no obvious differences in tear pharmacokinetics between twice daily and 3 times daily dosing regimens with no unexpected accumulation of lifitegrast in tears for these regimens.

2. Phase 3 Study 1118-DRY-400 (SONATA):

Title: A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Safety of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye (SONATA)

Name of Investigational Product: Lifitegrast ophthalmic solution (SAR 1118)

Study period: (First subject's consent to last subject's last protocol-defined assessment): 16 Oct 2012 to 03 Mar 2014

Objectives:
The primary objective of the study was:

- To evaluate the safety of lifitegrast ophthalmic solution (5.0%) compared to placebo 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).

The secondary objective of the study was:

- To evaluate the ocular safety measures of lifitegrast ophthalmic solution (5.0%) compared to placebo in subjects with dry eye when administered twice daily for 360 days (approximately 1 year).

The exploratory objectives of the study were:

- To assess clinical laboratory values (hematologic, renal, and liver panels) at Visit 1 (Day -7, Week -1) (baseline for safety clinical laboratory tests on all subjects who met entrance criteria), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) comparing subjects assigned to lifitegrast (5.0%) to placebo in approximately 25% (N=75) of study subjects

- To assess the concentration of lifitegrast in plasma 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 subjects assigned to lifitegrast (5.0%) in approximately 25% (N=75) of study subjects

- To assess CD3, CD4, and CD8 lymphocyte counts in whole blood at Visit 2 (Day 0, Month 0) (baseline for lymphocyte counts), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) comparing subjects assigned to lifitegrast (5.0%) to placebo in approximately 25% (N=75) of study subjects

- To assess corneal endothelial cell counts (specular microscopy) at Visit 2 (Day 0, Month 0) (baseline for corneal endothelial cell counts), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) comparing subjects assigned to lifitegrast (5.0%) to placebo in approximately 60% (N=180) of study subjects

- To evaluate AEs in subjects using lifitegrast in conjunction with other topical eye drops including artificial tears, steroids, mast cell stabilizers, and/or antihistamines

- To evaluate AEs in subjects using lifitegrast in conjunction with contact lenses.

Methodology:
This was a Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel-arm study conducted in the United States. Approximately 300 subjects with dry eye were planned to be randomized (2:1; lifitegrast:placebo) to receive either lifitegrast ophthalmic solution (5.0%) or placebo solution as topical ophthalmic drops administered bilaterally twice daily for 360 days (approximately 1 year).

Number of Subjects (Planned):
Approximately 300 subjects were planned to be randomized in a 2:1 ratio (lifitegrast:placebo).

Diagnosis and Main Criteria for Inclusion:

- Male or female, at least 18 years of age at the time of enrollment, with a subject-reported history of dry eye in both eyes
- Use and/or desire to use artificial tear substitute for symptoms of dry eye within past 6 months
- Best corrected visual acuity of 0.7 minimum angle of resolution 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)
- Corneal fluorescein staining score ≥2.0 (0-4 point scale) in at least 1 region in either eye at both Visits 1 and 2 (Days -7 and 0, Weeks -1 and 0)
- Visual analogue scale score ≥40 in either symptom of eye dryness or discomfort at Visit 1 (Day -7, Week 1)
- Schirmer Tear Test (without anesthesia) ≥1 and ≤10mm in either eye at Visit 1 (Day -7, Week -1)
- Subjects with secondary Sjögren's syndrome or other autoimmune diseases 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
- Subjects who electively used contact lenses may have participated in the study provided they:
    - 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)
    - Were not required to use contact lenses for medical reasons
    - 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
    - Had the contact lenses fitted >90 days prior to enrollment
    - Had no ongoing medical problems with the comfort or fit of the contact lenses
    - Did not anticipate any change in contact lenses or corrective eyeglasses in the next 12 months
    - Used only daily disposable lenses for this study.
- No ocular condition that, in the opinion of the investigator, could have affecte study parameters
- No use of any topical medication and/or antibiotics for the treatment of blephariti or meibomian gland disease
- No active or history of ocular herpes; any other ocular infection within the last 30 days
- No history of laser-assisted in situ keratomileusis 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
- No history of yttrium aluminum garnet laser capsulotomy within 6 months prior to Visit 1 (Day -7, Week -1)
- Subjects with dry eye secondary to scarring or destruction of conjunctival goblet cells were not eligible for the study. Subjects with incidental scars secondary to refractory 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.

Investigational Product, Dose, Mode of Administration, and Lot/Batch Number(s):
Lifitegrast 5.0% ophthalmic solution was administered twice daily to the ocular surface as a single eye dropin both eyes. The batch number for lifitegrast was 2F11.
Placebo ophthalmic solution was administered twice daily to the ocular surface as a single eye drop in both eyes. The batch numbers for placebo were 2E57 and 2E60.

Duration of Treatment:
The Screening Period was approximately 7 days and the Treatment Period was 360 days.

Criteria for Evaluation:
The trough concentration of lifitegrast in plasma was assessed at Visits 2, 5, and 7 (Days 0, 180, and 360;Months 0, 6, and 12) in approximately 25% of subjects (N=75).

No efficacy assessments were performed.

The following safety measurements were collected:

- Adverse events (ocular and non-ocular) (all visits)
- Clinical laboratory measurements (all subjects at Visit 1 [Day -7, Week -1]; approximately 25% of subjects at Visits 5 and 7 [Days 180 and 360, Months 6 and 12])
- Corneal fluorescein staining (all visits)
- Drop comfort (Visits 2-7 [Days 0-360, Months 0-12])
- Best corrected visual acuity (all visits)
- Slit lamp biomicroscopy (all visits)
- Dilated fundoscopy (Visits 1, 5, and 7 [Days -7, 180, and 360; Week -1, Months 6 and 12])
- Intraocular pressure (Visits 1, 5, and 7 [Days -7, 180, and 360; Week -1, Months 6 and 12])
- Lymphocyte counts (25% of subjects at Visits 2, 5, and 7 [Days 0, 180, and 360; Months 0, 6, and 12])
- Corneal endothelial cell counts (approximately 60% of subjects at Visits 2, 5, and 7 [Days 0, 180, and 360; Months 0, 6, and 12]).

Statistical Methods:

The Randomized Population included all randomized subjects. The Safety Population included all randomized subjects who received at least 1 dose of investigational product.

The study sample size was based on guidance provided by the United States Food and Drug Administration and is consistent with the International Conference on Harmonisation Guidance E1A on exposure for drugs intended for long-term treatment of non-life-threatening conditions. The sample size was not based on statistical calculations or statistical assumptions.

The primary safety assessment was based upon the percentage and severity of ocular and non-ocular treatment-emergent AEs (TEAEs). Adverse events were classified by the investigator as ocular (right eye, left eye, both) or non-ocular. Statistical analyses were descriptive in nature.

The secondary analyses consisted of a descriptive summary of safety measures (corneal fluorescein staining, best corrected visual acuity, slit lamp biomicroscopy, drop comfort, intraocular pressure, and dilated fundoscopy) by treatment at all measured time points.

The exploratory analyses consisted of descriptive statistics by treatment group produced for each of the following exploratory endpoints:

- Clinical laboratory values (all subjects at Visit 1 [Day -7, Week -1]; approximately 25% of subjects at
- Visits 5 and 7 [Days 180 and 360, Months 6 and 12])
- *Concentration of lifitegrast in plasma (approximately 25% of subjects)*
- *Lymphocyte counts (CD3, CD4, and CD8) (approximately 25% of subjects)*
- Corneal endothelial cell counts (approximately 60% of subjects)
- Use of artificial tears, topical ophthalmic steroids, topical antiallergy agents (mast cell stabilizers/antihistamines), and contact lenses for the purpose of evaluating AEs for subjects using these products.

Results:

Pharmacokinetic results:

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; Visits 2, 5, and 7).

Plasma Lifitegrast concentrations (Phase 3 SONATA: PK Subset)

	Lifitegrast N=220	
	n	Mean (SD), ng/mL
Day 0 (Month 0, Visit 2, baseline)	52	0.000 (0.0000)
Day 180 (Month 6, Visit 5)	47	0.308 (0.8264)
Day 360 (Month 12, Visit 7)	43	0.047 (0.2187)

Note: Sensitivity of detection is 0.50ng/mL.
SD=standard deviation
Source: SONATA Clinical Study Report, Section 14, Table 2.1

Reviewer's Comment:
If the reviewer assigns half-value of LLOQ (½ of 0.5 ng/mL) to patients with reported undetectable plasma lifitegrast concentrations, the estimated average plasma lifitegrast C_{trough} in this PK subset would be 0.52 ng/mL on Day 180 and 0.29 ng/mL on Day 360 (such values are slightly higher than those reported by the sponsor since patients with below LOQ plasma concentrations were assigned "0" concentrations values in the calculations).

Safety results:
Lifitegrast was generally well tolerated. The observed safety profile demonstrated no pattern of AE suggesting systemic toxicities or localized infectious complications due to chronic immunosuppression.

The lifitegrast group had a higher percentage of subjects with ocular TEAEs (53.6%) than the placebo group (34.2%), the majority of which were administration site TEAEs. The most common (>5%) TEAEs occurring in either treatment group were:

Ocular:
- Instillation site irritation (lifitegrast: 15.0%; placebo: 4.5%)
- Instillation site reaction (lifitegrast: 13.2%; placebo: 1.8%)
- Visual acuity reduced (lifitegrast: 11.4%; placebo: 6.3%)
- Dry eye (lifitegrast: 1.8%; placebo: 5.4%)

Non-ocular:
- Dysgeusia (lifitegrast: 16.4%; placebo: 1.8%)

The lifitegrast group had a higher frequency of subjects with ocular and non-ocular TEAEs considered probably related to the investigational product (26.4% and 15.9%, respectively) than the placebo group (6.3% and 2.7%, respectively). The frequency of subjects with ocular and non-ocular TEAEs considered not related or possibly related to the investigational product was similar between treatment groups. Most of the ocular and non-ocular TEAEs in both treatment groups were mild to moderate in severity.

One subject had a serious, non-ocular TEAE (arrhythmia) that resulted in death. There were no serious ocular TEAEs. Discontinuations due to TEAEs were infrequent (lifitegrast: 12.3%; placebo: 9.0%). The most common TEAEs that led to discontinuation were increased lacrimation, instillation site irritation, instillation site reaction, and dysgeusia.

After Visit 3 (Day 14, Week 2), subjects could have used artificial tears, topical ophthalmic or nasal steroids, antihistamines, mast cell stabilizers, and contact lenses as needed. Subjects in both treatment groups who used artificial tears had a higher frequency of TEAEs (placebo: 65.1%; lifitegrast: 85.9%) than subjects who did not use artificial tears (placebo: 41.8%; lifitegrast: 65.7%). Subjects who used artificial tears had a low rate of discontinuation due to TEAEs (placebo: 0%; lifitegrast: 3.1%). Few subjects used topical ophthalmic or nasal steroids, antihistamines, or mast cell stabilizers. Due to the small number of subjects who used topical ophthalmic or nasal steroids (placebo: 5 subjects; lifitegrast: 13 subjects), antihistamines or mast cell stabilizers (placebo: 5 subjects; lifitegrast: 10 subjects), and contact lenses (placebo: 4 subjects; lifitegrast: 5 subjects), no TEAE trends can be established. Within the subgroups of subjects who used artificial tears, topical ophthalmic or nasal steroids, antihistamines, mast cell stabilizers, and contact lenses, there were no trends signaling unique safety concerns between the 2 subgroups; the AE profile is consistent with that of the overall study population.

The other ocular safety parameters (corneal fluorescein staining, best corrected visual acuity, slit lamp biomicroscopy, dilated fundoscopy, intraocular pressure, and drop comfort) were comparable between the lifitegrast and placebo groups. Numerical improvements in drop comfort were observed over time in both treatment groups, but the lifitegrast group had consistently higher drop comfort scores (indicating a higher level of discomfort) than the placebo group.

In the hematologic, renal, and liver panels, the changes from baseline (Day -7, Week -1, Visit 1) to Days 180 and 360 (Months 6 and 12, Visits 5 and 7) were minimal and similar between treatment groups for all parameters.

The mean changes from baseline (Day 0, Month 0, Visit 2) to Days 180 and 360 (Months 6 and 12, Visits 5 and 7) in CD3, CD4, and CD8 counts were minimal and similar between treatment groups. The placebo group had slight numerical mean decreases and the lifitegrast group had slight numerical mean increases from Day 0 (Month 0, Visit 2) to Days 180 and 360 (Months 6 and 12, Visits 5 and 7) in corneal endothelial cell counts.

Reviewer's Comment:
Of the 9 patients with detectable plasma lifitegrast trough concentration on Day 180, and/or Day 360, two also had a potentially clinically important (PCI) reduction in lymphocyte count. However, the observed CD8 level in one of the 2 patients (Subject 45-021) on these days were either the same or higher as compared to the level taken at screening (pre-treatment). The other patient (Subject 45-041) had treatment emergent PCI lymphocyte count (also CD8 < 200/mcL) on Day 180 (level was not available for Day 360).

- Subject 45-021 (lifitegrast group) had PCI CD8 counts <220/μL at Days 180 and 360 (Months 6 and 12, Visits 5 and 7) (see following table).

Subject 45-021			
Laboratory Test	Day 0 Test Result (Month 0, Visit 2)	Day 180 Test Result (Month 6, Visit 5)	Day 360 Test Result (Month 12, Visit 7)
CD8	**120/μL**	**199/μL**	**196/μL**

- Subject 45-041 (lifitegrast group) had a PCI CD8 count <220/μL at Day 180 (Month 6, Visit 5) (see following table).

Subject 45-041			
Laboratory Test	Day 0 Test Result (Month 0, Visit 2)	Day 180 Test Result (Month 6, Visit 5)	Day 360 Test Result (Month 12, Visit 7)
CD8	271/μL	**208/μL**	Not available

Conclusions:

- Lifitegrast was generally well tolerated.
- The lifitegrast group had a higher frequency of subjects with ocular and non-ocular TEAEs than the placebo group.
- No serious ocular TEAEs were observed.
- Discontinuations due to TEAEs were infrequent.
- The ocular safety measures of lifitegrast were similar to placebo, as assessed by corneal fluorescein staining, best corrected visual acuity, slit lamp biomicroscopy, dilated fundoscopy, intraocular pressure, and drop comfort.
- The safety profile observed in this long-term study (360 days) was similar to that seen in the short-term studies (84 days); the increased treatment duration did not result in new risks.

Reviewer's Comments:
Two patients with plasma lifitegrast trough concentration above the EC_{50} necessary to inhibit by 50% T cell adhesion in vitro (>2.5 ng/mL) on Day 180 or Day 360, plus one additional patient with CD8 < 220/mcL did not experience clinically significant infections of immunosuppressive complications during the 12-month treatment period, suggesting the lack of a potential relationship among lifitegrast plasma concentrations, reductions in lymphocyte counts, and chronic immunosuppression following repeated topical ocular administration of the proposed product in dry eye disease patients .
One case of death (due to arrhythmia) was reported in the placebo group.

C. Consult Review (None)

D. Cover Sheet and OCP Filing/Review Form

25 February 2015

Renata Albrecht, M.D.
Division Director
Division of Transplant and Ophthalmology Drug Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road, Unit B
Beltsville, MD 20705

Product Name:	**Xiidra (Lifitegrast 5.0 % ophthalmic solution)**
NDA No.:	**NDA 208073**
Submission Type:	**Original NEW DRUG APPLICATION**
Sequence Number:	**0000**

Dear Dr. Albrecht:

In accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and Title 21 of the US Code of Federal Regulations (CFR), Part 314.50, Shire Development LLC (Shire) herewith submits an Original New Drug Application (NDA) for Xiidra (lifitegrast 5.0% ophthalmic solution, hereafter lifitegrast). Development of lifitegrast in the United States has been conducted under IND 077,885, originally submitted on 21 July 2008 (Serial No. 0000). This IND was originally submitted by SARcode Bioscience, Inc. (SARcode). SARcode was acquired by Shire on 17 April 2013.

The proposed indication for lifitegrast is for the treatment of signs and symptoms of dry eye disease (DED) (b) (4) administered twice a day (ie., AM and PM) into each eye using a single (b) (4). Despite the increasing understanding of the chronic inflammatory nature of ocular surface disease over the past 2 decades, there remains an unmet need for approved pharmacologic agents with faster onset of action that are well tolerated and that can improve both the signs and symptoms of dry eye in the United States.

Lifitegrast is a novel, potent, and selective anti-inflammatory small molecule antagonist of LFA-1 (also known as CD11a/CD18 or αLβ2) formulated as an unpreserved (b) (4) sterile eye drop. Lifitegrast binds to LFA-1 and prevents interaction with its cognate ligand, ICAM-1 (also known as CD54), thus inhibiting the leukocyte component of inflammation and immune activation including lymphocyte adhesion, infiltration, proliferation, and cytokine release. ICAM-1 is over-expressed in corneal and conjunctival tissues in dry eye disease. *In vitro* studies have demonstrated that lifitegrast inhibits T-cell adhesion to ICAM-1 expressing cells and inhibits secretion of key inflammatory cytokines (IFNγ, TNFα, IL-2) as well as inhibiting other pro-inflammatory cytokines: IL-1α, IL-1β, IL-2,IL-4, IL-5, and IL-13), all of which are known to be associated with dry eye disease.

Dry eye disease is a common and challenging problem for both clinicians and patients. Current treatments include artificial tears, punctal plugs, and cyclosporine. Despite the increasing understanding of the chronic inflammatory nature of ocular surface disease over the past 2 decades, there is an unmet need for pharmacologic agents approved to treat the symptoms associated with DED, the most common complaint of DED patients.

NONCLINICAL

The nonclinical program is in line with guidance provided in ICH M3 to support the chronic ocular administration dosing and as agreed in discussions with the FDA during development (refer to Module 1.6.3). The results of the nonclinical safety studies showed no significant adverse ocular or systemic toxicological findings or evidence of genotoxicity. Given the lack of in vitro and in vivo mutagenic effects and the low systemic exposure following topical ocular administration, carcinogenicity studies were not conducted.

CLINICAL

The lifitegrast DED clinical development program consists of: 1 clinical study in healthy subjects and 3 multicenter, prospective, randomized, double-masked, placebo-controlled safety and efficacy studies: 1 Phase 2 (1118-KCS-100) and 2 Phase 3 (1118-KCS-200 and 1118-DRY-300, hereafter referred to as OPUS-1 and OPUS-2, respectively), and 1 long-term multicenter, prospective, randomized, double-masked, placebo-controlled safety study (1118-DRY-400; hereafter referred to as SONATA). The efficacy of lifitegrast in the treatment of signs of DED was demonstrated in Studies 1118-KCS-100 (Phase 2) and OPUS-1, and the efficacy in treatment of the symptoms was demonstrated in Studies 1118-KCS-100 Phase 2) (not pre-specified) and OPUS-2. All were multicenter, prospective, randomized, double-masked, placebo-controlled safety and efficacy studies. A total of 1,536 subjects with DED have participated in clinical efficacy studies, with 823 of these exposed to lifitegrast.

Each of three 12-week studies were 14 weeks in duration with 5 study visits divided into a 2-week open-label placebo run-in screening period followed by a 12-week treatment period. In all three studies, the treatment schedule was twice daily (ie., AM and PM) topical administration of masked investigational product (lifitegrast or placebo). A treatment period of 12 weeks was chosen to allow a sufficient time to demonstrate improvements in signs and symptoms for subjects with DED. No concomitant use of artificial tears was allowed during the screening or treatment periods but all patients in OPUS-2 had a history of artificial tear use.

SONATA was a Phase 3, multicenter, randomized, double-masked and placebo-controlled study conducted in the United States comparing the safety of lifitegrast 5.0% in which subjects were instructed to follow a twice daily dosing regimen for 1 year (360 days). A total of 332 subjects were randomized to either lifitegrast or placebo (2:1). Refer to Module 2.7.3, Section 1.2 for additional details regarding the study designs of the clinical efficacy studies.

At the 15 May 2014 pre-NDA meeting, Shire presented the results of the above referenced clinical development program and the Agency indicated that the clinical portion of an NDA wit with the current clinical data package was fileable.

Based on the outcome of the pre-NDA meeting, Shire submitted a phase 3, multicenter, randomized, double-masked, and placebo controlled study on October 1, 2014 to IND 077,885. Shire is conducting the OPUS-3 study to provide additional data demonstrating improvement in symptoms associated with DED following twice daily administration with lifitegrast 5.0% for 12 weeks, focusing on DED patients with moderate to severe baseline symptomology (i.e. minimal baseline EDS score >60 and history of artificial tear use).

SUBMISSION COMPONENTS

As discussed and agreed in the 15 May 2014 Pre-NDA Meeting, Shire is providing the NDA in the International Conference on Harmonization (ICH) Common Technical Document (CTD) format. This submission contains the following five major sections.

NDA Submission

Module	Content
Module 1	Administrative Documents and Prescribing Information
Module 2	Common Technical Document Summaries
Module 3	Quality
Module 4	Nonclinical Study Reports
Module 5	Clinical Study Reports

Shire has provided the Summary of Clinical Efficacy (Module 2.7.3), and the Summary of Clinical Safety (Module 2.7.4) in Module 2 to satisfy the requirements for an Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), consistent with FDA's *April 2009 Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*. The integrated safety results (summary tables and analysis datasets) can be found in Module 5.3.5.3 (integrated summary of safety). A Clinical Overview is provided in Module 2.5. The agreed upon content of the statistical analysis plans for the ISE and ISS are located in Module 5.

Datasets

As discussed in the 15 May 2014 Pre-NDA Meeting, Shire is submitting the summary-level clinical site data for 4 studies (Study 1 [Phase2], Study 2 [OPUS-1], Study 3 [OPUS-2], and SONATA). A single summary-level dataset and DEFINE.pdf is provided in the format as described in the draft guidance "*Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning*" dated December 2012. The dataset contains the principal investigator name and information only. The MAXIMUM FINANCIAL DISCLOSURE AMOUNT and FINANCIAL DISCLOSURE INFORMATION are presented by principal investigator, but will reflect the financial disclosure information for all sub-investigators.

Additionally, as agreed Shire is submitting the 6 study's (Phase 1, Phase 2 DED, Phase 2 Allergic Conjunctivitis, OPUS-1, OPUS-2, SONATA) datasets in Clinical Data Interchange Standards Consortium Study Data Tabulation Model (Implementation Guide Version 3.1.2 or later) and Analysis Data Model (ADaM) Implementation Guide (Version 1.0 or later) format (including subject level analysis dataset) with associated metadata including the DEFINE.xml.

As agreed with the Agency during the Pre-NDA meeting, Shire did not submit patient profiles for these studies. The Statistical Analysis System programs for the studies (OPUS-1, OPUS-2, SONATA) deriving the ADaM datasets based on raw data are included in the NDA. Additionally, the programs for the primary efficacy and secondary efficacy analysis from ADaM data are included in the NDA. The analysis programs include the statistical models with the necessary data steps using the ADaM datasets as source.

MODULE 1 ADMINISTRATIVE INFORMATION

Labeling

Pursuant to §21 CFR 201.56 and 201.57, the product labeling contained in this NDA conforms to the requirements set forth by the 18 January 2006 *Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products.* Module 1 includes draft labeling (1.14.1.3 Draft Labeling Text), draft patient prescribing information (Patient Prescribing Information), annotated draft labeling (1.14.1.2 Annotated Draft Labeling Text), full color and scale product packaging (1.14.1.1 Draft Carton and Container Labels) along with the Structured Product Labeling (SPL).

Regulatory History

There have been 6 Type B meetings (3 Nonclinical/Clinical and 3 Chemistry, Manufacturing, and Controls [CMC]) to discuss the lifitegrast development program with the Agency since the IND was submitted on 21 July 2008. Agency correspondence (i.e., meeting minutes) is indicated and summarized in Module 1.6.3. The pre-IND correspondence is located in Module 1.12.1.

User Fee

In accordance with section 736 of the Federal Food, Drug and Cosmetic Act, Shire provided a Prescription Drug User Fee payment in the amount of $2,335,200.00 representing the total application fee for fiscal year 2015. The User Fee Cover Sheet, Form FDA 3397 (with User Fee I.D. Number PD3014602), and a copy of the check are enclosed as a reference (Module 1.1.3).

Field Copy Certification

In accordance with 21 CFR 314.50(d)(v), Shire hereby certifies that a letter had been provided to the FDA Philadelphia District office, (PHI-DO), at 900 US Customhouse, 200 Chestnut St., Philadelphia, PA 19106 notifying them that this NDA has been submitted. A copy of that letter can be found in Module 1.3.2.

Marketing Exclusivity

Shire Development LLC is claiming 5 years Waxman-Hatch Marketing Exclusivity under §21 CFR 314.108(b)(2) for the treatment of signs and symptoms of dry eye disease in adults. The active moiety in lifitegrast has not been approved in any drug product under section 505 of the Act. The exclusivity request is provided in Module 1.3.5.3.

Financial Disclosure and Debarment

As required in § 21 CRF 54.4, certification (Form FDA 3454) addressing the financial interests and arrangements for the clinical investigators who contributed to the Phase 2 and 3 clinical studies are enclosed in this application (Module 1.3.4). In addition, a certification statement is enclosed which states that Shire did not and will not use, in any capacity, the services of any person debarred under section 306(a) or (b) (Module 1.3.3).

Pediatric Waiver Request

In accordance with § 21 CFR 314.55 (c)(2), Shire is requesting a full waiver for the pediatric assessment of lifitegrast in the treatment of signs and symptoms of DED. The reasons for the request for a full waiver are that the necessary studies are impossible or highly impracticable to conduct. In a 22 July 2014 Advice Letter, the Agency indicated that they agreed with Shire's plan to request a full pediatric waiver. The Initial Pediatric Study Plan (iPSP) is provided in Module 1.9.1.

Tradename

Shire is submitting a request for the review of the proposed proprietary name, Xiidra (phonetically "ZYE-druh"). Provisional approval for Xiidra was received on 19 January 2014. In accordance with FDA's "Guidance for Industry: Contents of a Complete Submission for the Evaluation of Proprietary Names" (February 2010), appropriate supportive information regarding the product and proposed proprietary name is included in this application for consideration by the Agency. Please note the proposed labeling provided in this NDA should be used by the Division of Medication Errors and Prevention Analysis (DMEPA) for the proprietary name review.

Additional Information to Facilitate Review

The following additional documents have been included to facilitate your review of Chemistry Manufacturing and Controls (CMC) information located in Module 3:

- Annotated Table of Content (TOC) for Module 3.
- Summary of completed CMC commitments made to FDA during the PDUFA meetings.
- Disclosure and resolution of critical CMC issues.
- Demonstration of conformance with ONDQA filing checklist.

Safety Update

Shire will provide a 4-month safety update (4MSU) for this application on or before 27 June 2015. This safety update will consist of safety data available from the ongoing OPUS-3 study. OPUS-3 will be blinded at the time of the 4MSU and only approximately 40-50 subjects are anticipated to be completed by the cut off of no later than 17 April 2015. As agreed with Jacquelyn Smith, Senior Regulatory Project Manager, DTOP via e-mail on 19 December 2014, Shire will provide a "progress report" for OPUS-3 and any additional safety or new study information regarding the drug product from the literature, from competed studies, or from any ongoing studies to fulfill this requirement.

The totality of the data from the lifitegrast development program provides substantial evidence in support of and establishes that positive benefit-risk profile for an indication for the treatment of signs and symptoms of DED as the basis of this application.

CONFIDENTIALITY

This submission contains trade secrets and confidential commercial information exempt from public disclosure pursuant to Exemption 4 of the Freedom of Information Act and FDA regulations, and the disclosure of which is prohibited by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and other applicable law. Pursuant to FDA regulations, Shire Pharmaceuticals, Inc. is entitled to notice, an opportunity to object, and an opportunity to seek pre-release judicial review in the event that FDA determines that all or any part of this submission may be disclosed.

SUBMISSION TECHNICAL SPECIFICATIONS

This electronic submission is approximately 3.5 GB in total size. All files were checked and verified to be free of viruses prior to being sent via the Electronic Submissions Gateway. The files have been scanned using McAfee VirusScan Enterprise® Version 8.8 scan engine 5700.7163 and with a virus definition file version 7717.0000 created on February 19, 2015

Should you have any questions regarding this submission, please do not hesitate to contact me by telephone at (484) 595-8829, by facsimile at (484) 595-8156, or by email at kmccormick@shire.com; alternately, contact Bao Le, Associate Director, Regulatory Affairs, by telephone at (781) 482-1570, by facsimile at (781) 482-2958, or by email at ble@shire.com.

Sincerely,

Kimberly McCormick, PharmD
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CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	**NDA 208-073**	**SDN-1**	
Applicant	Shire Development LLC	**Submission Date**	25 February 2015
Generic Name	lifitegrast	**Brand Name**	Xiidra®
Drug Class	Anti-inflammatory topical agent; lymphocyte function-associated antigen-1 (LFA-1) antagonist		
Indication	Treatment of signs and symptoms of dry eye disease		
Dosage Regimen	One drop twice a day in each eye (b) (4)		
Dosage Form	Ophthalmic solution 5%	**Route of Administration**	Topical ocular
OCP Division	DCP4	**OND Division**	DTOP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Gerlie Gieser, PhD	Philip Colangelo, PharmD, PhD
Pharmacometrics		
Genomics		
Review Classification	☐ Standard ☑ Priority ☐ Expedited	
Filing Date	4/11/2015	**74-Day Letter Date** 5/10/2015
Review Due Date	7/28/2015	**PDUFA Goal Date** 8/25/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☐ Yes

☑ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☐ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☑ Metabolism Characterization		1	(primary hepatocytes of humans, animals)
☐ Transporter Characterization			(OATP study in rats)
☑ Distribution		1	(protein binding)
☑ Drug-Drug Interaction		1	CYP2C9 inhibition
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		
	☑ Multiple Dose	1	
Patients	☐ Single Dose		
	☑ Multiple Dose	1	C_{trough} collected in SONATA trial
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			

☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies		**In Vitro**	3	**In Vivo**	2
Total Number of Studies to be Reviewed			3		2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	See Biopharm review (SONATA trial used to-be-marketed formulation)
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	See Biopharm review for acceptability of biowaiver request
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the	☑Yes ☐No ☐N/A	

appropriate format (e.g., CDISC)?		
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Full waiver requested
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

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/s/

GERLIE GIESER
04/17/2015

PHILIP M COLANGELO
04/20/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	**NDA 208-073**	**SDN-1**	
Applicant	Shire Development LLC	**Submission Date**	25 February 2015
Generic Name	lifitegrast	**Brand Name**	Xiidra®
Drug Class	Anti-inflammatory topical agent; lymphocyte function-associated antigen-1 (LFA-1) antagonist		
Indication	Treatment of signs and symptoms of dry eye disease		
Dosage Regimen	One drop twice a day in each eye (b) (4)		
Dosage Form	Ophthalmic solution 5%	**Route of Administration**	Topical ocular
OCP Division	DCP4	**OND Division**	DTOP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Gerlie Gieser, PhD	Philip Colangelo, PharmD, PhD
Pharmacometrics		
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	4/26/2015	**74-Day Letter Date**	5/10/2015
Review Due Date	7/23/2015	**PDUFA Goal Date**	10/25/2015

Application Fileability

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☑ Yes

☐ No

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☑ No

If yes list comment(s)

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☑ No

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Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☐ Yes ☐ No
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Clinical Pharmacology Studies

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☐ Food Effect			
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Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		
	☑ Multiple Dose	1	
Patients	☐ Single Dose		
	☑ Multiple Dose	1	Lifitegrast C_{trough} collected at Months 6 and 12 in Phase 3 SONATA trial subset
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
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Total Number of Studies to be Reviewed		3		2

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/s/

GERLIE GIESER
03/19/2015

PHILIP M COLANGELO
03/19/2015