CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208073
Drug Name:	Xiidra (Lifitegrast Ophthalmic Solution, 5.0 %)
Indication(s):	For the treatment of signs and symptoms of dry eye disease (b) (4)
Applicant:	SHIRE DEVELOPMENT LLC
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1. EXECUTIVE SUMMARY

In this New Drug Application (NDA), the applicant seeks approval of Xiidra (lifitegrast ophthalmic solution 5.0%) for the treatment of the signs and symptoms of dry eye disease (DED) (b) (4). The NDA has two major submissions: the original NDA submitted on September 25, 2015 and the first re-submission on January 22, 2016. Efficacy and safety support for Xiidra in the original NDA was based on a Phase 2 and two Phase 3 studies (OPUS-1 and OPUS-2), and in the current NDA was based on a single Phase 3 study (OPUS-3).

All the studies included in the original and the current NDA were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild-to-moderate symptoms whereas the OPUS-2 and OPUS-3 studies enrolled subjects with moderate-to-severe symptoms. The studies were multicenter, randomized, double-masked, placebo-controlled studies. In all the studies, subjects were randomized to lifitegrast 5.0% (LIF 5.0%) or placebo in 1:1 ratio; the Phase 2 study included two additional lower strengths of lifitegrast (LIF 0.1% and 1.0%). Each study had a total duration of 14 weeks with two weeks placebo run-in period followed by 12 weeks treatment period. Efficacy data in each study were collected at Day 0 (baseline), Day 14, Day 42, and Day 84 with the primary efficacy variables in each study evaluated at Day 84.

The Phase 2 study defined a single primary efficacy endpoint for signs of DED, the OPUS-1 and OPUS-2 studies defined co-primary efficacy endpoints for sign and for symptom of DED, and the OPUS-3 study defined a single primary efficacy endpoint for symptom of DED. The primary sign endpoint in the Phase 2, OPUS-1, and OPUS-2 studies was the mean change in the inferior corneal staining score (ICSS; 0-4 scale) from baseline at Day 84. The primary symptom endpoint in the OPUS-1 study was the mean change in the visual-related function subscale of the Ocular Surface Disease Index (VR-OSDI; 0-4 scale) from baseline at Day 84; and in OPUS-2 and OPUS-3 was the mean change in the eye dryness score (EDS; 0-100 visual analogue scale) from baseline at Day 84.

The statistical review for the original NDA was finalized on July 22, 2015 (See Appendix 6.2). Based on the original NDA review, the Phase 3 studies did not demonstrate consistent efficacy results for the primary sign and symptom endpoints: OPUS-1 showed a significant treatment effect for sign ($p=0.0007$) but not for symptom ($p=0.8261$) whereas OPUS-2 showed a significant treatment effect for symptom ($p<0.0001$) but not for sign ($p=0.6122$). As a result, at the completion of the original NDA review, the review team concluded that there was a lack of substantial evidence to support Xiidra for the proposed indication, and recommended that an adequate and well controlled study be conducted to provide additional efficacy data. Consequently, on October 16, 2015, the applicant received a Complete Response Letter (CRL).

To address the deficiencies in the CRL and to support for approval, the applicant re-submitted the current NDA on January 22, 2016 with additional efficacy data from OPUS-3 study.

The primary objective of the OPUS-3 study was to evaluate the efficacy of Xiidra compared to placebo in improving the symptoms of DED measured in EDS; the study was primarily designed to re-produce the significant treatment effect for symptom seen in OPUS-2 study. In light of that, the study enrolled subjects with similar baseline characteristics as in OPUS-2 study and defined the same primary efficacy endpoint for symptom as in OPUS-2 study. Clinical sign of DED (as measured in ICSS) was defined in OPUS-3 study as a safety variable; however, for the purpose of across study assessment it was analyzed in this review as efficacy variable.

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The applicant main efficacy analyses in each study compared the mean change in EDS and the mean change in ICSS between the LIF 5% and Placebo treated groups, but the studies varied in the statistical analyses methods used to evaluate the treatment differences (See Table 2). As such, for ease of across study assessment, analysis of covariance (ANCOVA) model was used in this review to analyze all the studies.

i) Efficacy Evidence for Clinical Symptom of DED

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

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

Phase 2

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

Phase 3: OPUS-1

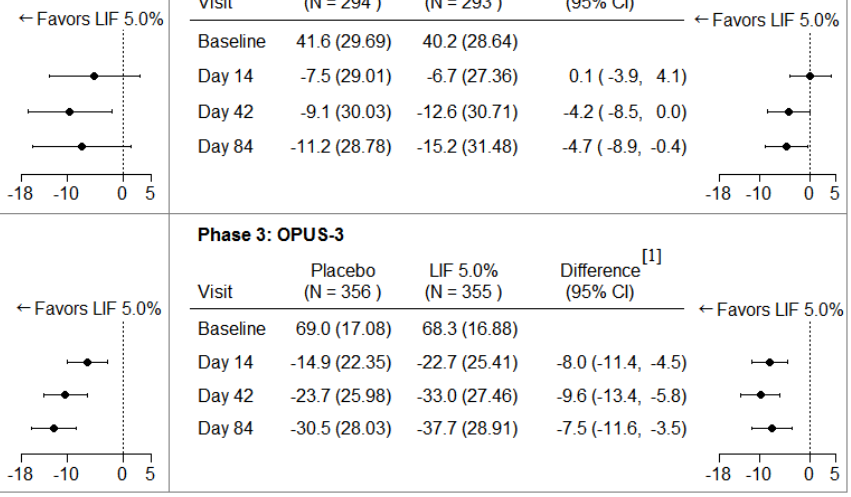
Visit	Placebo (N = 294)	LIF 5.0% (N = 293)	Difference[1] (95% CI)
Baseline	41.6 (29.69)	40.2 (28.64)	
Day 14	-7.5 (29.01)	-6.7 (27.36)	0.1 (-3.9, 4.1)
Day 42	-9.1 (30.03)	-12.6 (30.71)	-4.2 (-8.5, 0.0)
Day 84	-11.2 (28.78)	-15.2 (31.48)	-4.7 (-8.9, -0.4)

Phase 3: OPUS-2

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

Phase 3: OPUS-3

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



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

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

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

ii) Efficacy Evidence for Clinical Sign of DED

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

In the Phase 2 and OPUS-1 studies, placebo treated subjects showed worsening in clinical sign (as measured in ICSS) at Day 84 whereas LIF 5.0% treated subjects in these studies showed no change from baseline on average. In both studies, the mean reduction in ICSS at Day 84 in the

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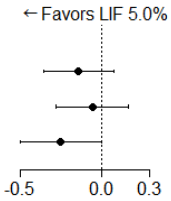
treatment arm was higher than in the placebo arm by about a quarter unit, and this difference was statistically significant in the OPUS-1 study ($p < 0.001$) and was marginally significant in the Phase 2 study ($p = 0.048$).

In the OPUS-2 and OPUS-3 studies, both placebo and LIF 5% treated subjects demonstrated at least half unit improvement early on (at Day 14) and continued improving throughout the study. At the end of the treatment period on Day 84; both groups in OPUS-2 study showed equal amount of improvement (about 0.7 units) from baseline on average, and LIF 5% treated group in OPUS-3 showed about 0.8 unit improvement from baseline while placebo treated group showed about 0.6 unit improvement from baseline.

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

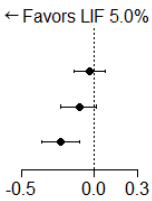
Phase 2

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



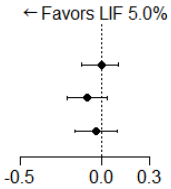
Phase 3: OPUS-1

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



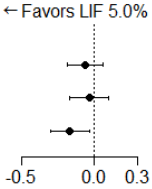
Phase 3: OPUS-2

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



Phase 3: OPUS-3

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



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

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

iii) Safety Evaluation

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

<u>Concluding Summary:</u>

Based on my review of the three studies included in the original NDA submission (Phase 2, OPUS-1, and OPUS-2) and the additional efficacy data from the OPUS-3 study, lifitegrast ophthalmic solution 5.0% demonstrated evidence of efficacy for the treatment of signs (as measured in ICSS) and symptoms (as measured in EDS) of dry eye disease (b) (4).

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2. INTRODUCTION

2.1 OVERVIEW

In this NDA re-submission, the applicant seeks approval of Xiidra for the treatment of signs and symptoms of dry eye disease. For detailed overview of the drug product, see Section 2.1 of the original NDA statistical review (Appendix 6.2).

2.1.1 Class and Indication

According to the applicant, lifitegrast ophthalmic solution 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 ophthalmic solution 5% is indicated for the treatment of the signs and symptoms of dry eye disease (b) (4).

2.1.2 History of Drug Development

The development of lifitegrast for the treatment of signs and symptoms of DED was submitted under initial IND 77885 on 21 July 2008. Since then several meetings were held with the Agency to discuss the development program.

The applicant submitted the original NDA for lifitegrast for the treatment of the signs and symptoms of DED (b) (4) on February 25, 2015. The submission included a Phase 2 dose-ranging and two Phase 3 (OPUS-1 and OPUS-2) efficacy and safety studies, and a Phase 3 safety study (SONATA). The statistical review for the original NDA was finalized on July 22, 2015 (See Appendix 6.2). Based on review of the studies included in the original NDA, the review team concluded that there was a lack of substantial evidence to support lifitegrast for the treatment of the signs and symptoms of DED, and recommended that an adequate and well controlled study be conducted to provide additional efficacy data. Consequently, at the conclusion of the Agency's review of the original NDA, the sponsor received a Complete Response Letter (CRL) on October 16, 2015.

The need for an additional clinical trial was discussed during the original Pre-NDA meeting held on May 15, 2015. Following the Pre-NDA meeting, the sponsor initiated a single Phase 3 study (OPUS-3) to evaluate the efficacy of lifitegrast 5% compared to placebo in improving the symptoms of DED with the signs of DED evaluated as safety variable.

On November 18, 2015, the applicant requested a Type A End-of Review Meeting with the objective to provide the Agency a summary of the OPUS-3 topline results and to provide their re-submission application format and content intended to address the deficiencies listed in the CRL to support approval. The Agency's preliminary Written Comment was submitted to the sponsor on 8 December 2015. In the December 8, 2015 written comments, the Agency requested that the results for the sign assessments be discussed in the OPUS-3 study report despite sign being defined in the study as a safety variable; with that in mind, the Agency agreed with the planned format and content of the resubmission to address the deficiencies in the CRL to support review.

On 22 January 2016, the sponsor re-submitted the NDA for lifitegrast ophthalmic solution 5%; the re-submission included the efficacy and safety data from the new OPUS-3 study.

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2.1.3 Specific Studies Reviewed

This NDA re-submission contained a single Phase 3 study (OPUS-3), and the primary focus of this review was on this study. The study was similar in design to the previous studies, and was conducted in 41 sites in the United States (US). The study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) - two weeks open label placebo run-in screening period followed by 12 weeks treatment period. Treatment in the study was administered as a single drop twice daily (AM and PM) in each eye for 12 weeks.

A total of 711 subjects were enrolled in 40 sites (one site did not enroll a single subject) all in the US. All subjects enrolled in this study had documented history of artificial tear use (ATU) within 30 days prior to the screening visit on Day -14 and EDS ≥ 40 at baseline. A brief summary of the study is presented in Table 1.

Table 1: Summary of OPUS-3 Study

Study ID/ Study Type	**Study Design / Primary Study Objective**	**Dose, Route and Regimen/ # of Patients**	**Duration of Treatment / Primary efficacy endpoint**	**Study Population**
SHP606-304 (OPUS-3) Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy compared to placebo as assessed by change from baseline in eye dryness score at Day 84, Day 42, and Day 14; and to evaluate safety and tolerability compared to placebo	Lifitegrast (LIF) 5.0% or Placebo ophthalmic solution; single drop BID LIF 5.0% (N = 355) Placebo (N = 356) **Total (N = 711)**	12 Weeks (84 Days) The study included a single primary efficacy endpoint for symptom of dry eye: The mean change in Eye Dryness Score (EDS) [0–100 point visual analogue scale (VAS) in both eyes] from baseline at Day 84. Key secondary efficacy endpoints: The mean change in EDS from baseline at Days 42 and 14.	• Subjects at least 18 years of age with dry eye disease. • Had a history of ATU within 30 days prior to the screening visit on Day -14 • Subjects with moderate-to-severe symptom (EDS ≥40)

Source: Applicant's Section 2.7.6: Synopses of Individual Studies

2.2 DATA SOURCES

The data source for this review included the clinical study report, the analysis and tabulation datasets, and the integrated summary of safety datasets. These were provided in electronic submission and are located at: \\cdsesub1\evsprod\nda208073\0019 for the NDA re-submission and at \\cdsesub1\evsprod\nda208073\0000 for the original NDA.

The data summarized in this review primarily covered the OPUS-3 study; the study was submitted to provide additional efficacy evidence for lifitegrast ophthalmic solution 5.0%.

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The NDA re-submission was provided in an electronic submission. It included, among other documents, the clinical study report, the finalized protocols (including amendments) and the statistical analysis plan, both analysis and tabulation datasets, and case report forms for few selected subjects. The SAS codes used to perform the analyses and to create the analysis datasets were also provided.

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There were no major issues identified with respect to the quality and integrity of the submitted data. Although the submitted datasets were not fully CDISC compliant, the submission included certain elements of the CDISC standards. In addition, the '*Reviewer's Guide Document'* and the '*Define.pdf*' files included in the submission package provided sufficient detail to access and to easily work with the datasets. Therefore, minimal efforts were needed to process the data and no additional support was required from other sources.

3.2 EVALUATION OF EFFICACY

3.2.1 Study Design and Endpoints

The primary objective of OPUS-3 study was to evaluate the efficacy of lifitegrast 5.0% compared to placebo in improving the symptom of DED (as measured in EDS). The study was designed similar to all the studies included in the original NDA submission, but it enrolled subjects with similar baseline characteristics as in OPUS-2 study. For more detail on the design of the OPUS-3 study, see design description of the studies included in the original NDA (Section 3.2.1 of the statistical review for original NDA in Appendix 6.2).

The OPUS-3 study was primarily designed to evaluate the efficacy of lifitegrast compared to placebo in improving the clinical symptom of DED (as measured in EDS), and to re-produce the treatment effect for symptom seen in the OPUS-2 study - note that lifitegrast 5.0% demonstrated significant improvement in clinical symptom (as measured in EDS) compared to placebo in the OPUS-2 study. As such, the OPUS-3 study defined the same symptom endpoint as OPUS-2 study; the primary efficacy endpoint for symptom in OPUS-3 study was the mean change in EDS from baseline at Day 84. The mean change in EDS from baseline at Days 42 and 14 were defined as key secondary endpoints in the study. In OPUS-3 study, the signs of DED (as measured by: corneal fluorescein staining, conjunctival staining with lissamine green, and schirmer tear test) were defined as safety variables.

It should be noted that efficacy data for the signs of DED were collected from both eyes but analysis was based on a study eye whereas a single efficacy data was collected for the symptoms of DED regardless of the study eye. See Section 3.2.1 of the original NDA statistical review for the 'study eye' definition (Appendix 6.2).

3.2.2 Statistical Methodology

The protocol-defined main efficacy analysis in each study compared the clinical sign (as measured in ICSS) and clinical symptom (as measured in EDS) improvement achieved at day 84 between the study arms. However, as shown in Table 2, the studies varied in the endpoint definition, the missing data approach, and the statistical analyses methods used to evaluate the treatment differences. As such, for ease of across study comparison, the reviewer used the same statistical analysis method and the same missing data handling approach to analyze all the studies included in the original and current NDA.

The reviewer main efficacy analysis approach used analysis of covariance (ANCOVA) model. In the ANCOVA model, the change in EDS (the change in ICSS) from baseline at Day 84 was used as the response variable; and treatment, baseline EDS (baseline ICSS), and stratification factor (specific to the Phase 3 studies) were used as covariates in the model. The ANCOVA model in all the studies was based on the ITT population with LOCF used for imputing missing data (including baseline values if all post-baseline values were missing).

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Based on the ANCOVA model, the treatment differences for the mean change in EDS (in ICSS) was determined using the least square means; the default observed margin (OM) option was used in the LSMEANS statement of the PROC MIXED procedure in SAS.

Table 2: Summary of the Primary Efficacy Endpoints and Applicant's Statistical Analysis Methods

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

ITT = intent-to-treat; LOCF=last observation carried forward; ICSS = inferior corneal staining score; VR-OSDI=visual related function subscale of Ocular Surface Disease Index; EDS=eye dryness score

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

Several sensitivity analyses were also performed under different missing data handling approaches to assess the robustness of the primary efficacy results that used LOCF for missing data:

i) ANCOVA model using observed data (without missing data imputation) and using worst observation carried forward (WOCF) for imputing missing data.

ii) A mixed model repeated measure analysis (MMRM) using observed data, and

The sensitivity analyses results were consistent with the primary efficacy analysis results that used LOCF (See Section 3.2.4.4).

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Table 3: Number of Subjects with Available Efficacy Data by Visit
(ITT Population)

			Baseline	Day 14	Day 42	Day 84	Have only Baseline Value
Phase 2	EDS	Placebo	58	54	49	47	**3**
		LIF 5.0%	57*	54	51	48	**4**
	ICSS	Placebo	58	55	50	47	**3**
		LIF 5.0%	58	54	52	48	**4**
OPUS-1	EDS	Placebo	295	291	288	283	3
		LIF 5.0%	293	287	281	281	6
	ICSS	Placebo	294**	290	287	283	3
		LIF 5.0%	293	287	281	281	6
OPUS-2	EDS	Placebo	360	359	354	350	0
		LIF 5.0%	358	357	341	328	1
	ICSS	Placebo	360	359	354	350	0
		LIF 5.0%	358	356	340	328	2
OPUS-3	EDS	Placebo	356	353	338	327	**3**
		LIF 5.0%	355	352	341	321	**2**
	ICSS	Placebo	356	351	338	327	**5**
		LIF 5.0%	355	350	341	322	**4**

* One subject (Subject ID = 001-1227) who did not have a baseline EDS value was excluded from efficacy analysis;
** One subject who did not have a study eye designated was excluded from analysis.

Reference ID: 3938302

3.2.3 Patient Disposition, Demographics, and Baseline Disease Characteristics

3.2.3.1 Patient Disposition

The summary of patient disposition and the primary reasons for study discontinuation during the 12-week treatment period are shown in Table 4 for each study. The results for the Phase 2, OPUS-1, and OPUS-2 studies were also presented here for the purpose of across study assessment - see Section 3.2.3.1 of the original NDA statistical review for detailed discussion on these studies (Appendix 6.2).

Table 4: Disposition of Patients and Reasons for Study Discontinuation
(All Randomized Subjects)

	Phase 2		**OPUS-1**		**OPUS-2**		**OPUS-3**	
	Placebo (N = 58)	LIF 5.0% (N = 58)	Placebo (N = 295)	LIF 5.0% (N = 293)	Placebo (N = 360)	LIF 5.0% (N = 358)	Placebo (N = 356)	LIF 5.0% (N = 355)
Number of randomized and treated subjects (ITT Population) [1]	58 (100)	58 (100)	295 (100)	293 (100)	360 (100.0)	358 (100.0)	356 (100)	355 (100)
Safety Population	58 (100.0)	58 (100.0)	295 (100)	293 (100)	359 (99.7)	359 (100.3)	354 (99.4)	357 (100.6)
Per-protocol Population	44 (75.9)	46 (79.3)	265 (89.8)	246 (84.0)	NA	NA	NA	NA
Subjects who completed the study	48 (82.8)	48 (82.8)	284 (96.3)	281 (95.9)	348 (96.7)	321 (89.7)	318 (89.3)	319 (89.9)
Subjects discontinued from the study	10 (17.2)	10 (17.2)	11 (3.7)	12 (4.1)	12 (3.3)	37 (10.3)	38 (10.7)	36 (10.1)
Reason for withdrawal								
Adverse event	1 (1.7)	6 (10.3)	3 (1.0)	10 (3.4)	3 (0.8)	26 (7.3)	9 (2.5)	22 (6.2)
Erroneously Admitted	0	0	0	0	0	0	7 (2.0)	4 (1.1)
Lost to follow-up	2 (3.4)	1 (1.7)	2 (0.7)	0	0	2 (0.6)	4 (1.1)	2 (0.6)
Non-compliance	1 (1.7)	1 (1.7)	2 (0.7)	0	0	1 (0.3)	5 (1.4)	2 (0.6)
Pregnancy	0	0	1 (0.3)	0	0	0	0	0
Other	6 (10.3)	2 (3.4)	3 (1.0)	2 (0.7)	9 (2.5)	8 (2.2)	13 (3.7)	6 (1.7)

Source: Table 3 of Phase 2, OPUS-1, and OPUS-2 and Table 4 of OPUS-3 Clinical Study Reports. LIF 5.0% = lifitegrast 5.0% ophthalmic solution
[1] The ITT population in the Phase 2 study included all randomized subjects

A total of 711 subjects were randomized in OPUS-3 study, and 74 (10.4%) subjects discontinued before the Week 12 treatment period; the discontinuation rate in each treatment group was about 10%. Adverse event (AE) was the most common reason for discontinuation in the LIF 5.0% treated group (6% versus 3% in Placebo), and most of the subjects that were discontinued due to AE in this group did so due to *burning, stinging, or blurred vision upon instillation of study drop*.

For each study, the discontinuation rate over time is shown in Figure 3; note that, the discontinuation rates between the study arms in OPUS-3 study were indistinguishable throughout the treatment period.

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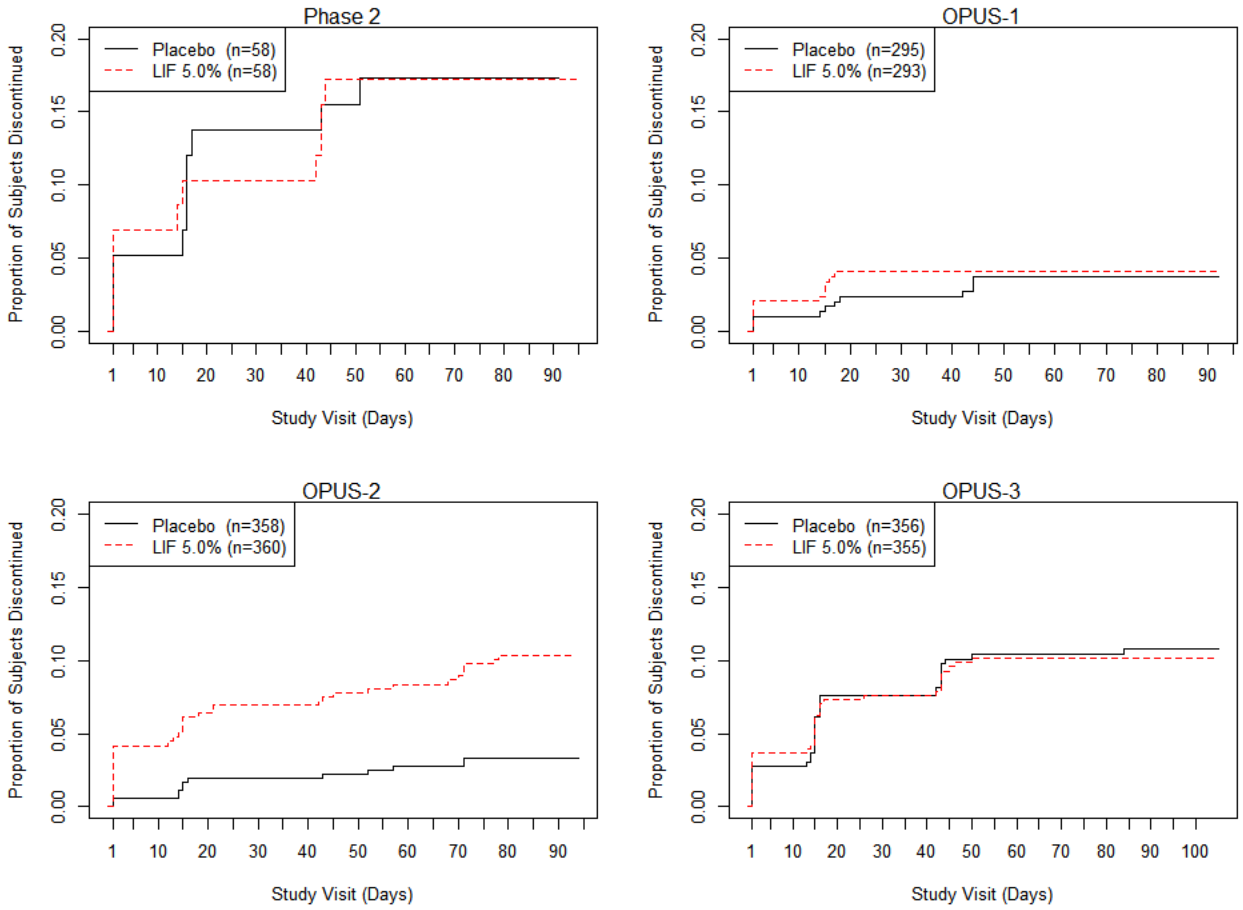
Figure 3: Proportion of Subjects Discontinued from Study
(All Randomized Subjects)



3.2.3.2 Demography

The summary of demographic and baseline disease characteristics for subjects in the ITT population are presented in Table 5 and Table 6, respectively - the demographic and baseline disease characteristics within each study were well balanced between the treatment groups. The summaries for the Phase 2, OPUS-1, and OPUS-2 studies were presented here for the purpose of across study assessment - see Sections 3.2.3.2 and 3.2.3.3 of the original NDA statistical review for detailed discussion on these studies (Appendix 6.2).

The demographic and baseline disease characteristics in OPUS-3 study were very similar to that of OPUS-2 study – note that OPUS-3 study was designed similar to OPUS-2 study. As such, the majority of subjects in OPUS-3 study were white (≥75%), more than 75% were female, and the average age of patients was about 60 years with 37% of patients ≥65 years.

All subjects in the OPUS-3 study (as in OPUS-2 study) had a documented history of artificial tear use and EDS ≥ 40 at baseline; the mean baseline EDS in the study was about 68 and about 65% of the subjects had baseline EDS ≥60. In terms of the baseline clinical sign, the mean ICSS at baseline was 2.5 units, and about 85% of subjects in this study had baseline ICSS above 1.5 units.

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Table 5: Demographic Summary by Study and Treatment Group
(ITT Population)

	Phase 2		OPUS-1		OPUS-2		OPUS-3	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 358)**	**LIF 5.0% (N = 360)**	**Placebo (N = 356)**	**LIF 5.0% (N = 355)**
Age								
Mean (SD)	60.4 (12.93)	62.3 (12.22)	61.1 (11.77)	60.2 (12.21)	58.9 (14.26)	58.7 (13.93)	58.6 (14.84)	58.8 (14.10)
Median	60.5	62.0	62.0	59.0	60.5	59.4	61.0	60.0
Range	26.0, 89.0	31.0, 85.0	24.0, 85.0	20.0, 91.0	19.8, 88.7	19.2, 97.5	18.0, 93.0	19.0, 87.0
Age Group, n (%)								
>= 65	18 (31.0)	23 (39.7)	117 (39.7)	99 (33.8)	135 (37.5)	122 (34.1)	137 (38.5)	128 (36.1)
Sex, n (%)								
Female	45 (77.6)	47 (81.0)	217 (73.6)	229 (78.2)	265 (73.6)	285 (79.6)	269 (75.6)	268 (75.5)
Male	13 (22.4)	11 (19.0)	78 (26.4)	64 (21.8)	95 (26.4)	73 (20.4)	87 (24.4)	87 (24.5)
Ethnicity, n (%)								
Hispanic or Latino	0 (0.0)	0 (0.0)	7 (2.4)	6 (2.0)	64 (17.8)	79 (22.1)	58 (16.3)	60 (16.9)
Not Hispanic or Latino	58 (100)	58 (100)	288 (97.6)	287 (98.0)	296 (82.2)	279 (77.9)	298 (83.7)	295 (83.1)
Race, n (%)								
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	2 (0.6)	4 (1.1)	0 (0.0)	2 (0.6)
Asian	1 (1.7)	3 (5.2)	2 (0.7)	3 (1.0)	14 (3.9)	19 (5.3)	24 (6.7)	24 (6.8)
Black or African American	3 (5.2)	2 (3.4)	11 (3.7)	16 (5.5)	34 (9.4)	30 (8.4)	47 (13.2)	48 (13.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	2 (0.6)	1 (0.3)	2 (0.6)
White	54 (93.1)	53 (91.4)	276 (93.6)	270 (92.2)	305 (84.7)	303 (84.6)	279 (78.4)	265 (74.6)
Other	0 (0.0)	0 (0.0)	4 (1.4)	3 (1.0)	2 (0.6)	0 (0.0)	5 (1.4)	14 (3.9)
Iris Color, n (%)								
Black	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)	6 (1.7)	3 (0.8)
Blue	20 (34.5)	21 (36.2)	98 (33.2)	105 (35.8)	86 (23.9)	80 (22.3)	70 (19.7)	70 (19.7)
Brown	21 (36.2)	18 (31.0)	96 (32.5)	113 (38.6)	189 (52.5)	193 (53.9)	194 (54.5)	199 (56.1)
Gray	1 (1.7)	1 (1.7)	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)	5 (1.4)	2 (0.6)
Green	6 (10.3)	3 (5.2)	27 (9.2)	18 (6.1)	35 (9.7)	27 (7.5)	25 (7.0)	34 (9.6)
Hazel	10 (17.2)	15 (25.9)	71 (24.1)	52 (17.7)	49 (13.6)	56 (15.6)	56 (15.7)	47 (13.2)
Other: Blue/Brown	--	--	0 (0.0)	1 (0.3)	--	--	--	--
Missing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	--	--	--	--
Artificial Tear Use, n (%) [1]								
Yes	29 (50.0)	31 (53.4)	130 (44.1)	128 (43.7)	360 (100)	358 (100)	356 (100)	355 (100)

Source: Table 4 of Phase 2, OPUS-1, and OPUS-2 and Table 5 of OPUS-3 Clinical Study Reports; [1] Based on reviewer analysis

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Table 6: Baseline Disease Characteristics by Study and Treatment Group
(ITT Population)

	Phase 2		OPUS-1		OPUS-2		OPUS-3	
Parameters	**Placebo (N = 58)**	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 360)**	**LIF 5.0% (N = 358)**	**Placebo (N = 356)**	**LIF 5.0% (N = 355)**
ICSS:								
Mean	1.6 (0.51)	1.8 (0.51)	1.8 (0.60)	1.8 (0.60)	2.4 (0.72)	2.4 (0.76)	2.5 (0.75)	2.5 (0.68)
Median	2.0	2.0	2.0	2.0	2.5	2.5	2.5	2.5
Range	0.5, 2.5	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 4.0	0.5, 4 0	0.5, 4 0	0 5, 4.0
ICSS Category, n (%)								
≤ 1.5	22 (37.9)	19 (32.8)	105 (35.7)	95 (32.4)	47 (13.1)	46 (12.8)	46 (12.9)	37 (10.4)
> 1.5	36 (62.1)	39 (67.2)	189 (64.3)	198 (67.6)	313 (86.9)	312 (87.2)	310 (87.1)	318 (89.6)
Total CSS								
Mean	4.4 (1.20)	4.3 (1.06)	4.8 (1.38)	4.8 (1.40)	5.2 (2.01)	5.1 (2.08)	5.5 (2.02)	5.3 (1.84)
Median	4.3	4.0	4.5	4.5	4.5	4.5	5	5
Range	1.0, 7.0	2.5, 7.5	2.0, 9.5	2.0, 10.0	1.0, 11.5	1.0, 12.0	0.5, 11.5	1.0, 10.5
Nasal CLGSS:								
Mean	1.80 (0.93)	1.69 (0.77)	1.90 (0.84)	2.03 (0.81)	2.14 (1.05)	2.13 (1.04)	2.1 (0.98)	2.1 (0.97)
Median	2.00	2.00	2.00	2.00	2.50	2.00	2	2
Range	0.0, 4.0	0.0, 3.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0 0, 4.0	0.0, 4 0	0 0, 4.0
STT (Un-anesthetized):								
Mean	4.7 (2.84)	5.0 (2.98)	4.7 (2.86)	4.9 (3.01)	5.1 (2.77)	5.5 (2.83)	5.2 (2.70)	5.0 (2.65)
Median	4.0	5.0	4.0	4.0	5.0	5.0	5	5
Range	1.0, 10.0	1.0, 10.0	1.0, 10.0	1.0, 10.0	0.0, 10.0	1.0, 10.0	1.0, 10.0	1.0, 11.0
EDS:								
Mean	51.8 (23.55)	51.6 (24.69)	41.6 (29.69)	40.2 (28.64)	69.2 (16.76)	69.7 (16.95)	69.0 (17.08)	68.3 (16.88)
Median	55.0	51.0	39.0	42.0	69.0	69.0	69.0	67.0
Range	0.0, 98.0	3.0, 100.0	0.0, 100.0	0.0, 100.0	40.0, 100.0	40.0, 100 0	40.0, 100.0	40.0, 100.0
EDS Category, n (%)								
< 40 [1]	17 (29.3)	19 (32.8)	148 (50.2)	137 (46.8)	NA	NA	NA	NA
40 – 50	7 (12.1)	7 (12.1)	20 (6.8)	28 (9.6)	52 (14.4)	43 (12.0)	43 (12.1)	50 (14.1)
50 – 60	11 (19.0)	10 (17.2)	45 (15.3)	55 (18.8)	67 (18.6)	76 (21.2)	86 (24.2)	75 (21.1)
≥ 60	23 (39.7)	22 (37.9)	82 (27.8)	73 (24.9)	241 (66.9)	239 (66.8)	227 (63.8)	230 (64.8)

[1] EDS ≥ 40 at Days -14 and 0 was required in the OPUS-2 and OPUS-3 studies;
ICSS: Inferior corneal staining score; Total CSS: Total corneal staining score; Nasal CLGSS: Nasal conjunctival lissamine green staining score; STT: Schirmer Tear Test (mm/5 minutes); EDS: Eye Dryness Score (VAS);

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The distributions of the baseline ICSS and EDS values in each study are shown in Figure 4 and Figure 5, respectively. Note that the Phase 2 and OPUS-1 studies enrolled subject with mild-to-moderate symptom in severity; and as such, all subjects in these studies by design had ICSS 0.5 – 3.0 and EDS ≥0 at baseline – about 30% and 45% of subjects in the Phase 2 and OPUS-1 studies, respectively, had baseline EDS < 40. The OPUS-2 and OPUS-3 studies, on the other hand, enrolled subjects with moderate-to-severe symptom in severity; and as such, all subjects in these studies by design had ICSS 0.5 – 4.0 and EDS ≥ 40 at baseline – note that at least 10% of subjects in each study had ICSS > 3.0 at baseline.

Figure 4: Distribution of ICSS at Baseline (ITT Population)

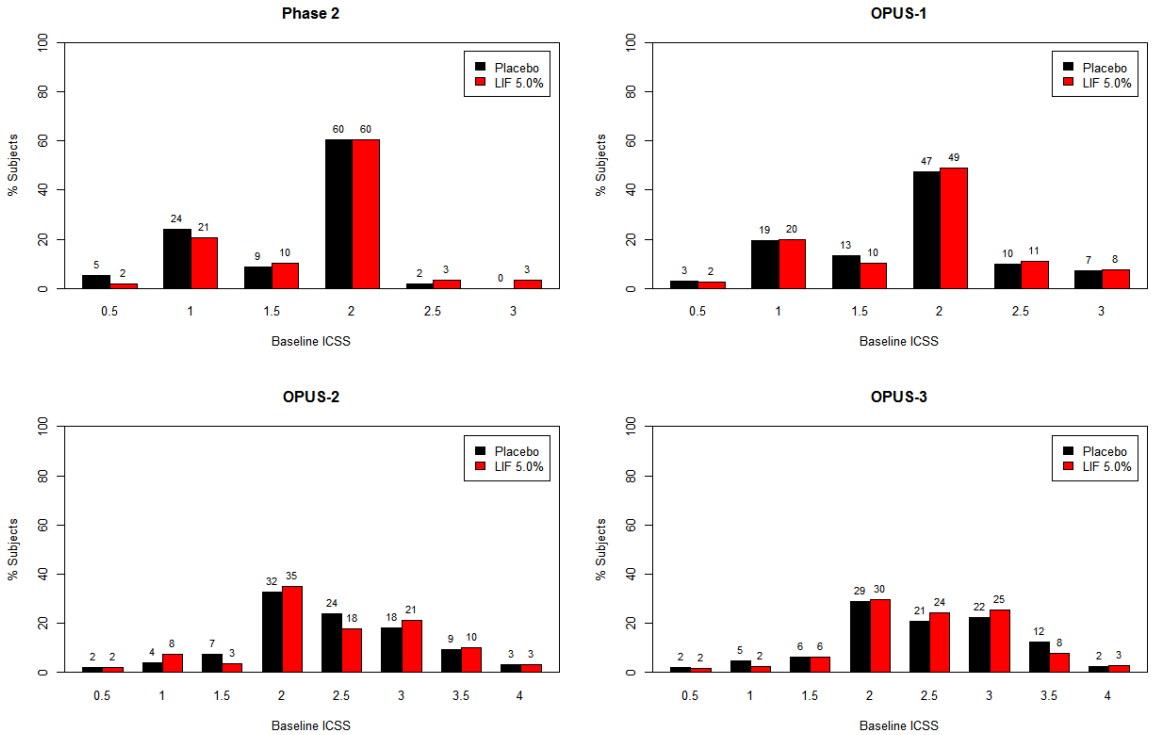
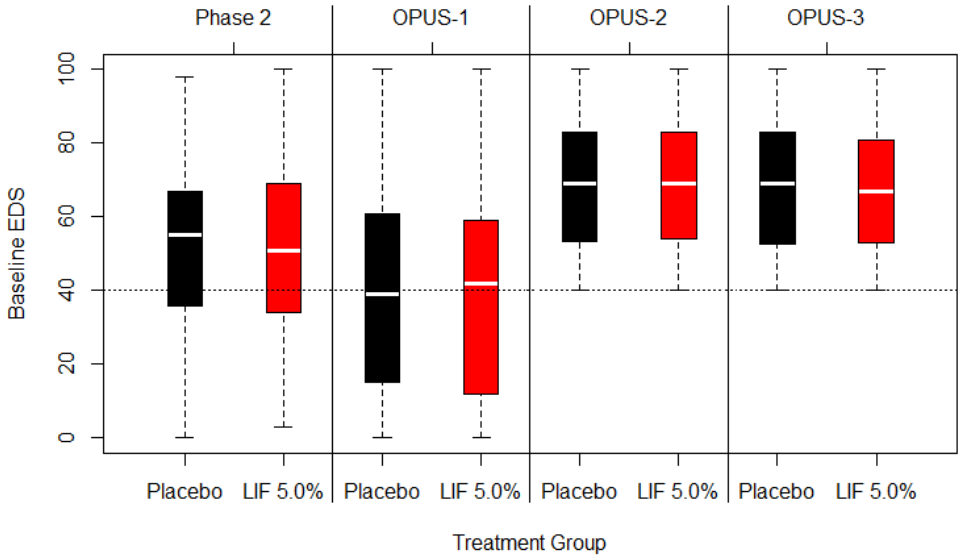


Figure 5: Distribution of EDS at Baseline (ITT Population)



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3.2.4 Efficacy Results and Conclusions

In this section the efficay results are discussed for the OPUS-3 study. The efficacy results for the Phase 2, OPUS-1, and OPUS-2 studies were discussed in the statistical review for the original NDA submission (See Section 3.2.4 in Appendix 6.2); the high level efficacy findings from these studies were as follows:

Studies	Clinical Sign (as measured in ICSS) [1]	Cinical Symptom:
OPUS-1	Superiority in improving the clinical sign of DED was demonstrated at Day 84	• Superiority in improving clinical symptom of dry eye (as measured in VR_OSDI: co-primary symptom endpoint) was NOT demonstrated • Large improvement in clinical symptom (as measured in EDS) was seen in the treatment arm compared to in the placebo arm in a subgroup of subjects with a recent history of ATU and baseline EDS ≥40.
OPUS-2	Superiority in improving the clinical sign of DED was NOT demonstrated at Day 84; however, both study arms showed large improvement in clinical sign throughout the study.	• Superiority in improving clinical symptom of DED (as measured in EDS: co-primary symptom endpoint) was demonstrated • The study enrolled subjects with a recent history of ATU and baseline EDS ≥40, and EDS was used as the symptom endpoint in the study based on the efficacy results seen in a subgroup of subjects with a recent history of ATU and baseline EDS ≥40 in OPUS-1 study
Phase 2	• Superiority was NOT demonstrated at Day 84; however, a dose-response was seen at Day 84. • The treatment difference seen in this study was very close to what was seen in OPUS-1: the lack superiority was likely due to smaller sample size compared to OPUS-1 study.	• Although clincial symptom endpoint was not defined in the Phase 2 study, the treatment arm in the study showed better improvement in clinical symptom (as measured in VR_OSDI as well as in EDS) compared to Placebo. • Furthermore, the study showed a dose-response in both clinical symptom measures (VR_OSID and EDS) at Day 84.

[1] The mean change in ICSS from baseline at Day 84 was the primary sign endpoint in each study. VR_OSDI: visual-related function subscale of the Ocular Surface Disease Index (0-4 scale)

In the following sections, the efficacy results for the signs (as measured in ICSS) and for the symptoms (as measured in EDS) of DED are discussed for the OPUS-3 study – the efficacy results for the Phase 2, OPUS-1, and OPUS-2 studies were also presented for across study assessment.

It should be noted that since the signs of DED were defined as safety variable in OPUS-3 study, confidence intervals and p-values for all sign related variables in this study were intended for descriptive use only.

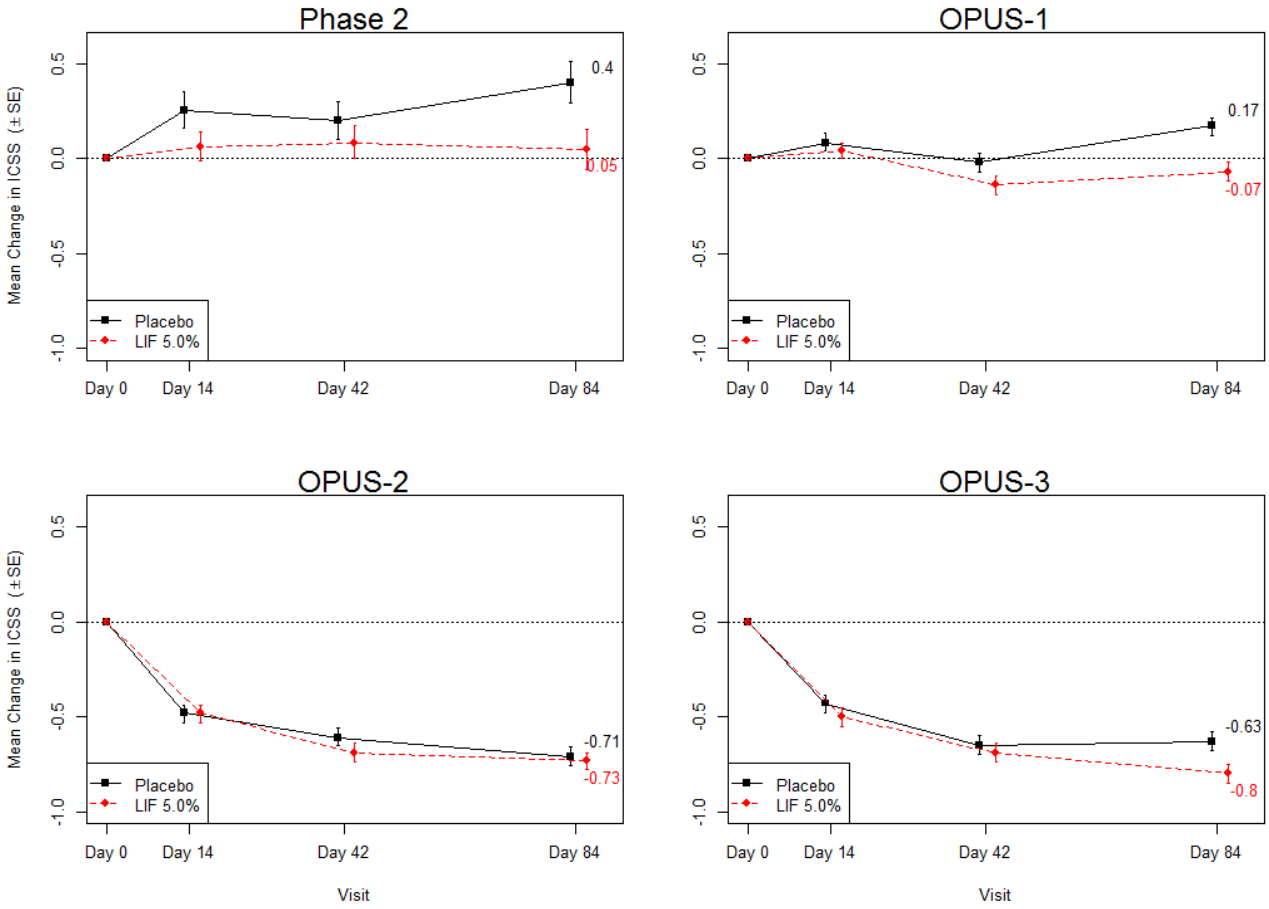
3.2.4.1 Efficacy Results for Signs of DED as Measured in ICSS

The mean changes in ICSS from baseline (± SE) over time are shown in Figure 6 below for each study. Both study arms in OPUS-3 study showed at least half unit improvement in ICSS early on (at Day 14) and continued throughout the study as was also seen in OPUS-2 study.

Reference ID: 3938302

At the end of the treatment period on Day 84; both groups in OPUS-2 showed equal amount of improvement (about 0.7 units) from baseline on average whereas LIF 5% treated group in OPUS-3 showed about 0.8 unit improvement while placebo showed about 0.6 unit improvement.

Figure 6: Mean Change (±SE) in ICSS from Baseline at each Visit
(ITT Population, LOCF)



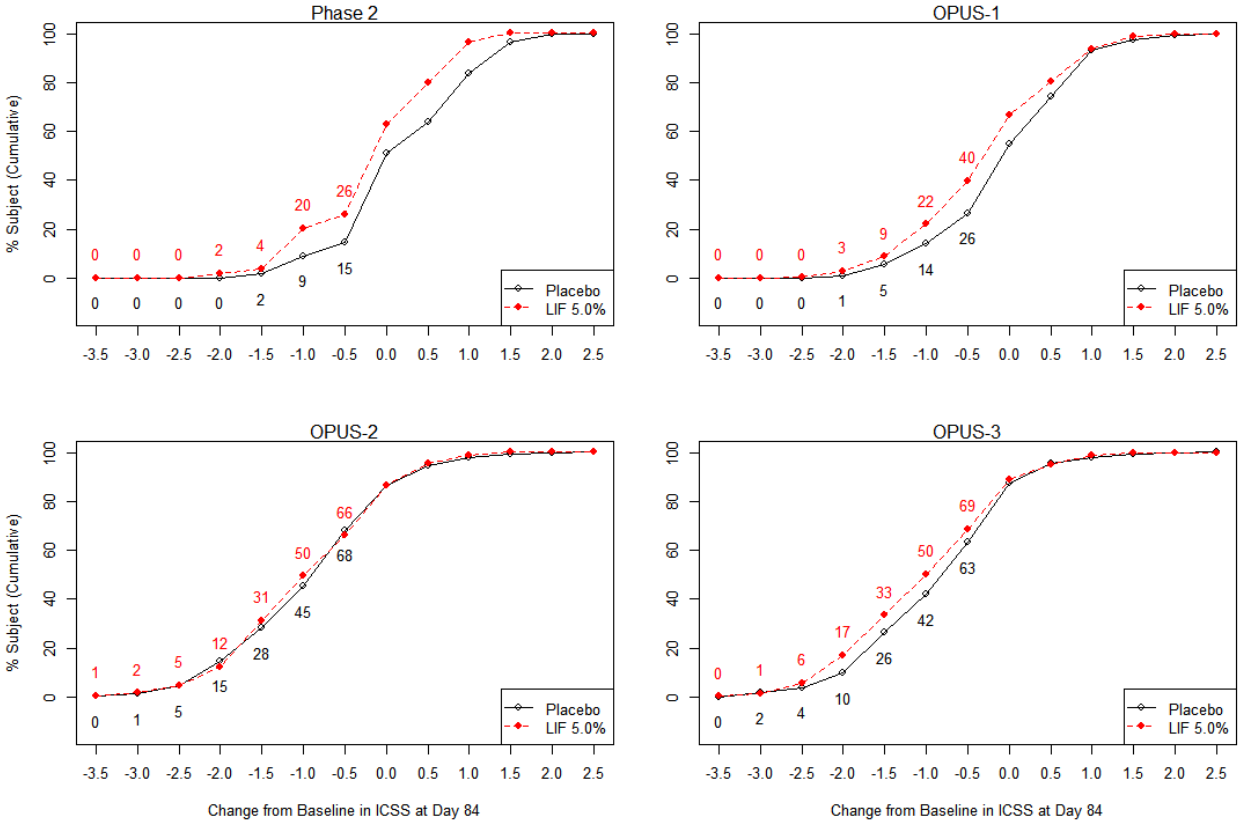
In Figure 7 below, the cumulative distributions of the change in ICSS from baseline at Day 84 are shown for each study.

In OPUS-3 study, slightly more LIF 5% treated subjects showed some form of reduction in ICSS at Day 84 compared to those in the placebo arm; for example, about 50% and 17% of subjects in the LIF 5% treated group showed improvement in ICSS by at least one and two units at Day 84, respectively, compared to 42% and 10% of subjects in the placebo treated group.

Treatment comparison for the proportion subjects with ≥ 1 unit and ≥ 2 units improvement in ICSS from baseline at day 84 was shown for each study in Table 10.

Reference ID: 3938302

Figure 7: Cumulative Distribution of the Change in ICSS from Baseline at Day 84
(ITT Population, LOCF)



The summary of ICSS at baseline and Day 84, and the change from baseline at Day 84 are shown in Table 7. Both study arms in the OPUS-3 study showed improvement in ICSS throughout the study as was seen in OPUS-2 study. However, the treatment arm in OPUS-3 showed a slightly better improvement at Day 84 compared to the placebo arm: the mean change in ICSS at Day 84 in the treatment arm was -0.80 (-0.90, -0.70) and in the placebo arm was -0.63 (-0.73, -0.54); the treatment difference was -0.17 (95% CI: -0.30, -0.03; p-value = 0.0135).

The mean changes in ICSS from baseline at Days 14 and 42 were also compared between the study arms in OPUS-3 study, and the improvements seen at these visits were the same between the study arms (See Figure 2).

In summary, based on the totality of evidence, LIF 5.0% demonstrated efficacy benefit in maintaining or improving the clinical sign of dry eye (as measured in ICSS) than placebo.

- In the Phase 2 and OPUS-1 studies, the mean reduction in ICSS at Day 84 in LIF 5% treated group was higher than in the placebo treated group by about a quarter unit, and this difference was statistically superior in the OPUS-1 study and was marginally significant in the Phase 2 study (p = 0.049).
- Both groups in OPUS-2 showed equal amount of improvement (about 0.7 units) from baseline on average, and LIF 5.0% in OPUS-3 showed about 0.8 unit improvement while placebo showed about 0.6 unit improvement. The treatment difference in the mean reduction in ICSS in the OPUS-3 study was statistically significant even though sign was not defined as efficacy variable in the study.

Reference ID: 3938302

Table 7: Summary of Mean Change in ICSS from Baseline at Day 84
(ITT Population, LOCF)

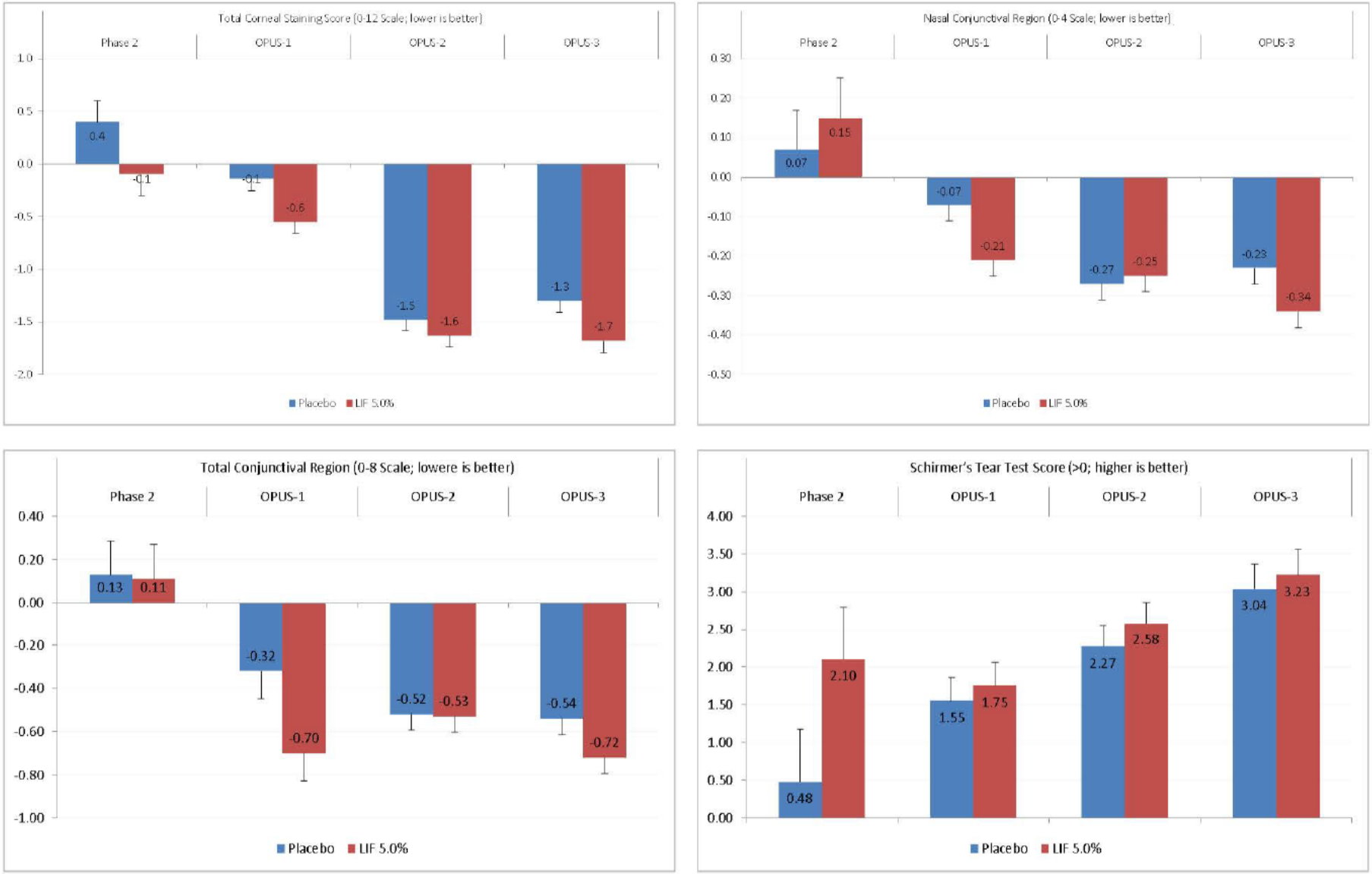
	Phase 2		OPUS-1		OPUS-2		OPUS-3	
Summary	**Placebo (N=58)**	**LIF 5.0% (N=58)**	**Placebo (N=294)**	**LIF 5.0% (N=293)**	**Placebo (N=360)**	**LIF 5.0% (N=358)**	**Placebo (N=356)**	**LIF 5.0% (N=355)**
Baseline								
Mean (SD)	1.65 (0.513)	1.77 (0.515)	1.81 (0.599)	1.84 (0.597)	2.40 (0.722)	2.39 (0.763)	2.46 (0.746)	2.46 (0.681)
Median	2.00	2.00	2.00	2.00	2.50	2.50	2.50	2.50
(95% CI)	(1.51, 1.78)	(1.63, 1.90)	(1.75, 1.88)	(1.78, 1.91)	(2.33, 2.47)	(2.31, 2.47)	(2.38, 2.53)	(2.39, 2.53)
Day 84								
Mean (SD)	2.03 (0.710)	1.81 (0.674)	1.98 (0.874)	1.77 (0.879)	1.69 (1.010)	1.66 (1.044)	1.82 (1.013)	1.66 (1.039)
Median	2.00	2.00	2.00	2.00	1.50	1.50	2.00	1.50
(95% CI)	(1.84, 2.21)	(1.63, 1.99)	(1.88, 2.08))	(1.67, 1.87)	(1.59, 1.80)	(1.55, 1.77)	(1.72, 1.93)	(1.55, 1.77)
Change from Baseline to Day 84								
Mean (SD)	0.38 (0.785)	0.04 (0.745)	0.17 (0.819)	-0.07 (0.868)	-0.71 (0.943)	-0.73 (0.926)	-0.63 (0.911)	-0.80 (0.939)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50	-0.50	-1.00
95% CI	(0.17, 0.59)	(-0.15, 0.24)	(0.07, 0.26)	(-0.17, -0.04)	(-0.80, -0.61)	(-0.83, -0.64)	(-0.73, -0.54)	(-0.90, -0.70)
Based on adjusted analysis [1]:								
LS Means (SE)	0.34 (0.089)	0.09 (0.089)	0.16 (0.05)	-0.07 (0.05)	-0.7 (0.047)	-0.7 (0.05)	-0.63 (0.048)	-0.80 (0.048)
Diff.(minus Placebo) (95% CI)		-0.25 (-0.50, -0.00)		-0.23 (-0.36, -0.09)		-0.03 (-0.16, 0.10)		-0.17 (-0.30, -0.03)
P-value: ANCOVA		0.0498		0.0007		0.6122		0.0135
Based on unadjusted analysis:								
P-value: Student T-test		0.0197		0.0007		0.6768		0.0149
P-value: Wilcoxon Test		0.0386		0.0006		0.7849		0.0167

[1] Based on ANCOVA model that adjusted for the baseline ICSS in the phase 2 study, and for the baseline ICSS and stratification factors in OPUS-1, OPUS-2, and OPUS-3 studies.

The effect of the drug product on other clinical sign variables (*e.g., total corneal staining score [0-12 scale], nasal conjunctival region [0-4 scale], total conjunctival region [0-8 scale], and Schrimer's Tear Test Score [>0]*) was also assessed in each study. As shown in Figure 8 below, the drug product also demonstrated numerical improvement in these variables compared to placebo.

Reference ID: 3938302

Figure 8: Mean Change from Baseline in Other Clinical Sign Variables at Day 84
(ITT Population; LOCF)



Reference ID: 3938302

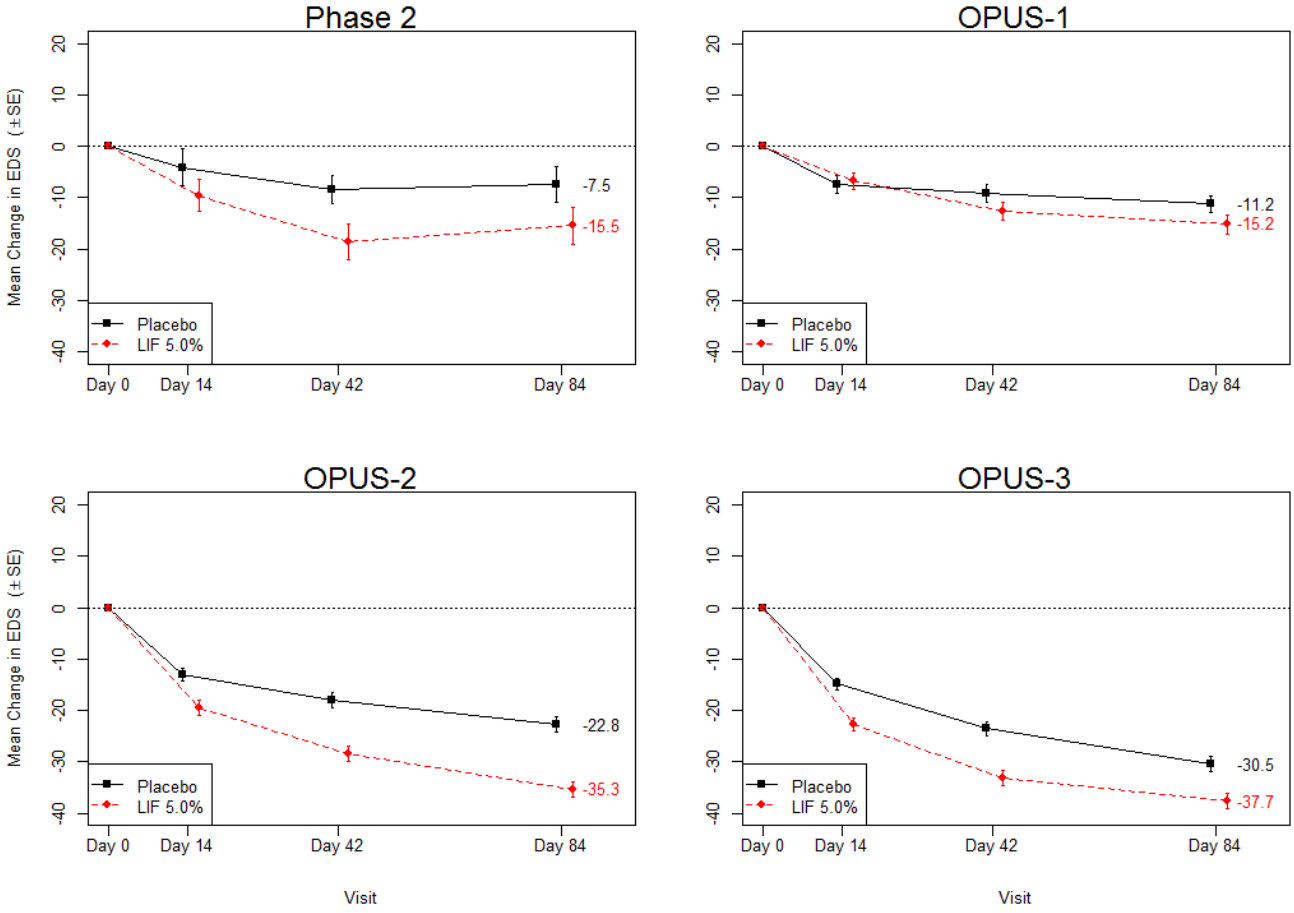
3.2.4.2 Efficacy Results for Symptom of DED as Measured in EDS

The mean change in EDS from baseline at Day 84 was defined as the single primary efficacy endpoint for the symptoms of DED in OPUS-3 study. The same endpoint was defined as co-primary symptom endpoint in OPUS-2 study, and as supportive symptom endpoint in the Phase 2 and OPUS-1 studies. The results for the Phase 2, OPUS-1, and OPUS-2 studies were discussed in detail in the original NDA statistical review (See Section 3.2.4 Appendix 6.2).

The summary of the mean change in EDS from baseline over time are shown in Figure 9 below for each study – the Phase 2, OPUS-1, and OPUS-2 study results were included for across study assessment.

As was seen in the OPUS-2 study, both study arms in OPUS-3 study demonstrated improvement in EDS throughout the study; however, the improvement seen in the treatment arm in these studies was larger than in the placebo arm throughout the study. For example, the improvement seen in the treatment arm at Day 84 was higher than in the placebo arm by about 12 units in OPUS-2 and by about 8 units in OPUS-3.

Figure 9: Mean Change in EDS (± SE) from Baseline at each Visit
(ITT Population, LOCF)



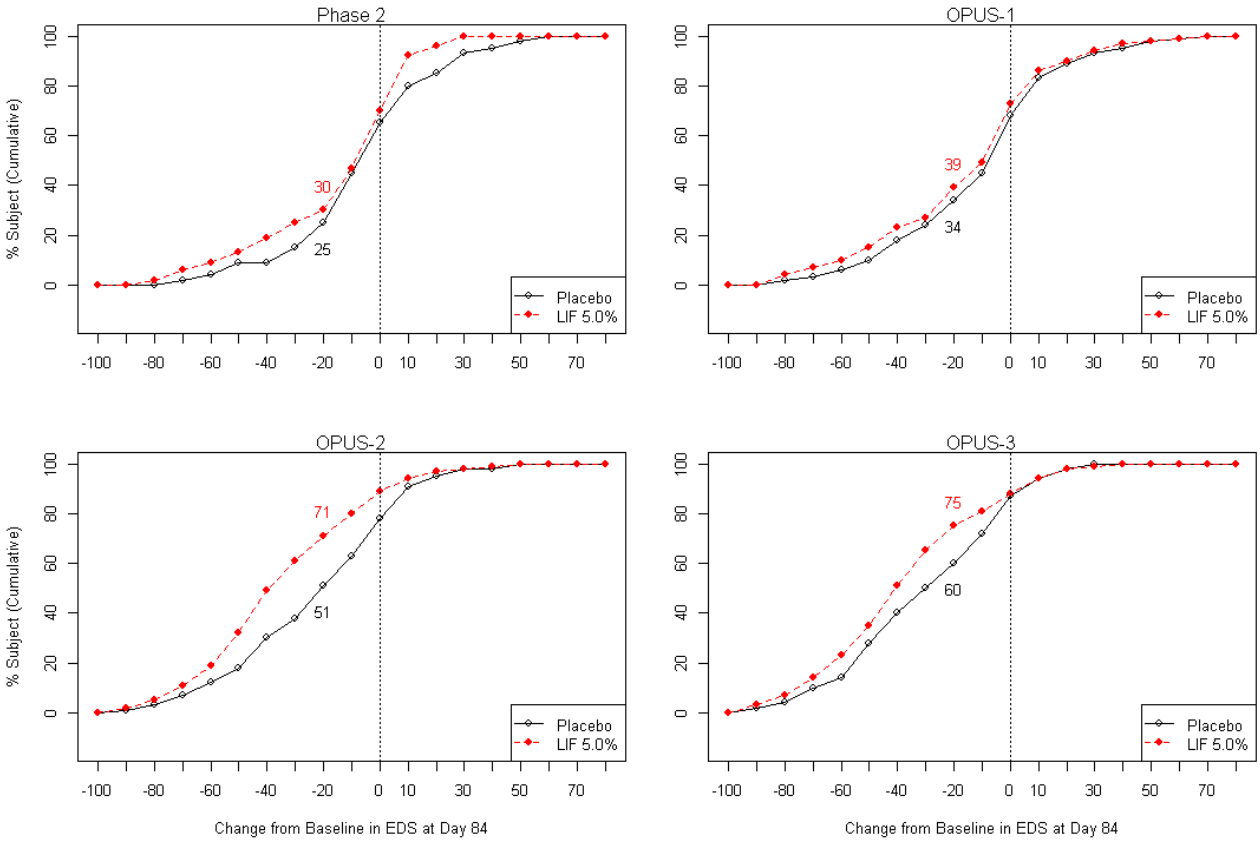
To further explore the level of improvement in clinical symptom achieved at Day 84, the cumulative distribution for the change in EDS from baseline at Day 84 was summarized in Figure 10 below for each study.

Reference ID: 3938302

In OPUS-3 study, as was seen in OPUS-2 study, more subjects in the treatment arm showed improvement in EDS at Day 84 compared to subjects in the placebo arm; for example, in the OPUS-2 and OPUS-3 studies, respectively, about 20% and 15% more subjects in the treatment arm showed improvement in EDS by at least 20 units compared to subjects in the placebo arm.

Treatment comparison for the proportion subjects with ≥ 10 and ≥ 20 units improvement in EDS from baseline at day 84 was shown for each study in Table 11.

Figure 10: Cumulative Distribution of Change in EDS from Baseline at Day 84
(ITT Population, LOCF)



The summary of the EDS data at baseline and Day 84, and the change from baseline at Day 84 are shown in Table 8. As was stated earlier, both study arms in OPUS-3 study demonstrated improvement in EDS at Day 84; however, the improvement seen in the treatment arm was larger than in the placebo arm by about 8 units. In this study, the mean change in EDS at Day 84 was -38 (95% CI: -41, -35) in the treatment arm and was -31 (95% CI: -33, -28) in the placebo arm; the treatment difference was -8 (95% CI: -12, -4) and was strongly statistically significant (p-value = 0.0003).

Note that the treatment arm displayed significant improvement in EDS as early as day 14 and continued throughout the treatment period (See Figure 1).

In summary, based on the primary efficacy evidences seen in OPUS-2 and OPUS-3 studies and the supportive evidences seen in the Phase 2 and OPUS-1 studies, the drug product showed efficacy evidence in improving the clinical symptom of dry eye disease (as measured in EDS) compared to placebo.

Reference ID: 3938302

Table 8: Summary of Mean Change in EDS from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2		OPUS-3	
Summary	**Placebo (N = 58)**	**LIF 5.0% (N = 57)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 360)**	**LIF 5.0% (N = 358)**	**Placebo (N = 356)**	**LIF 5.0% (N = 355)**
Baseline								
Mean (SD)	51.8 (23.55)	51.6 (24.69)	41.6 (29.69)	40.2 (28.65)	69.2 (16.76)	69.7 (16.95)	68.9 (17.08)	68.3 (16.88)
Median	55.00	51.00	39.00	42.00	69.00	69.00	69.0	67.00
(95% CI)	(45.6, 58.0)	(45.0, 58.1)	(38.2, 45.0)	(36.9, 43.5)	(67.5, 70.9)	(67.9, 71.4)	(67.2, 70.7)	(66.6, 70.1)
Day 84								
Mean (SD)	44.7 (26.93)	37.3 (28.15)	30.4 (30.77)	25.0 (28.87)	46.5 (29.88)	34.4 (27.86)	38.5 (29.91)	30.6 (27.73)
Median	47.00	34.00	19.00	11.00	50.00	28.00	39.00	23.0
(95% CI)	(37.6, 51.7)	(29.9, 44.7)	(26.9, 33.9)	(21.9, 28.3)	(43.4, 49.6)	(31.5, 37.3)	(35.4, 41.6)	(27.8, 33.6)
Change from Baseline to Day 84								
Mean (SD)	-7.2 (25.29)	-14.4 (25.36)	-11.2 (28.78)	-15.2 (31.48)	-22.8 (28.60)	-35.3 (28.40)	-30.5 (28.03)	-37.7 (28.91)
Median	-6.00	-6.00	-6.00	-9.00	-20.00	-39.00	-29.50	-41.00
(95% CI)	(-13.8, -0.5)	(-21.1, -7.7)	(-14.5, -7.9)	(-18.8, -11.6)	(-25.7, -19.8)	(-38.3, -32.3)	(-33.4, -27.6)	(-40.7, -34.6)
Based on adjusted analysis [1]:								
LS Means (SE)	-7.1 (3.10)	-14.4 (3.12)	-10.9 (1.53)	-15.5 (1.54)	-22.9 (1.45)	-35.2 (1.45)	-30.3 (1.45)	-37.8 (1.45)
Diff.(minus Placebo) (95% CI)		-7.3 (-16.1, 1.4)		-4.7 (-8.9, -0.4)		-12.3 (-16.4, -8.30)		-7.53 (-11.6, -3.50)
P-value: ANCOVA		0.0980		0.0311		<0.0001		0.0003
Based on un-adjusted analysis:								
P-value: Student T-test		0.1277		0.1137		<0.0001		0.0008
P-value: Wilcoxon Test		0.3231		0.1376		<0.0001		0.0004

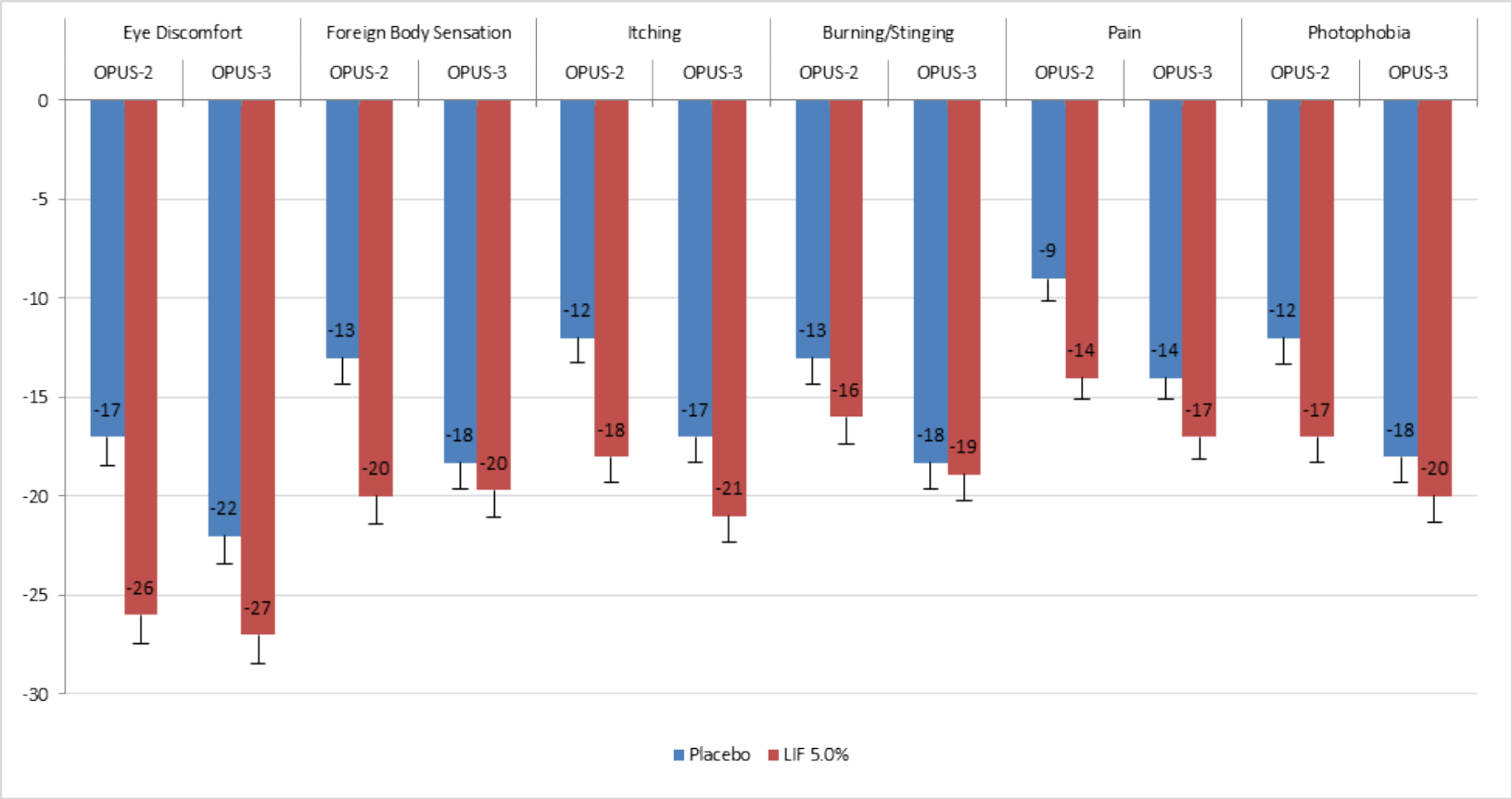
[1] Based on ANCOVA model that adjusted for baseline EDS in the phase 2 study, and for baseline EDS and stratification factors in the OPUS-1, OPUS-2, and OPUS-3 studies.

Reference ID: 3938302

The effect of the drug product in improving other clinical symptom parameters (*such as: Eye Discomfort, Foreign Body Sensation, Itching, Burning/Stinging, Pain, and Photophobia all measured in a VAS scale [0-100]*) were also assessed.

As shown in Figure 11 below (for the OPUS-2 and OPUS-3 studies), the drug product clearly demonstrated numerically better improvement in these symptom parameters of DED as well compared to placebo.

Figure 11: Mean Change (±SE) in Other Clinical Symptom Variables at Day 84
(ITT Population, LOCF)



Note: All the clinical symptom parameters listed in the figure were measured in visual analogue scale (0 - 100; 0 = no discomfort and 100 = maximal discomfort)

Reference ID: 3938302

3.2.4.3 Relationship between Clinical Sign and Clinical Symptom of Dry Eye

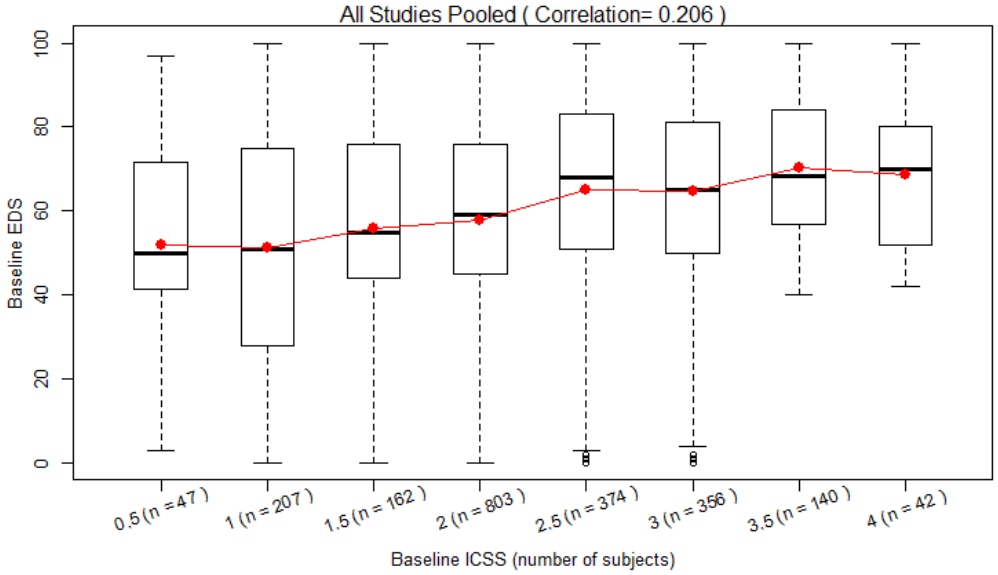
The clinical studies summarized in the original and the current NDA submission did not demonstrate consistent efficacy results for the clinical sign (as measured in ICSS) and for the clinical symptom (as measured in EDS) of DED. For example, OPUS-1 showed significant treatment effect for sign but not for symptom whereas OPUS-2 showed significant treatment effect for symptom but not for sign. OPUS-3, on the other hand, showed significant treatment effect for both sign and symptom even though sign was defined in the study as a safety variable.

To further understand the relationship between the sign and symptom of DED, the relationship between the ICSS and EDS data before treatment was received (at baseline) and after treatment was received (at day 84) were explored based on the pooled data from the four studies.

a) Relationship between ICSS and EDS at Baseline (Before treatment was received)

To assess the relationship between the sign and the symptom of DED at baseline (i.e., before treatment was received), the distributions of the EDS data at baseline were presented by the unique baseline ICSS values in Figure 12.

Figure 12: Distribution of EDS by ICSS at Baseline
(ITT Population)



Note 1: Both study arms were pooled to assess the relationship at baseline assessment,
Note 2: Baseline ICSS score of 3.5 and 4.0 were from OPUS-2 and OPUS-3 studies only
Note: Dots and lines in red were for mean EDS values at baseline

Clearly, the relationship between the baseline ICSS and EDS data in the overall pooled data was weak (correlation = 0.20); that is, a slight increase in the average EDS (i.e., worsening in clinical symptom) was observed with increasing ICSS values (i.e., worsening in clinical sign).

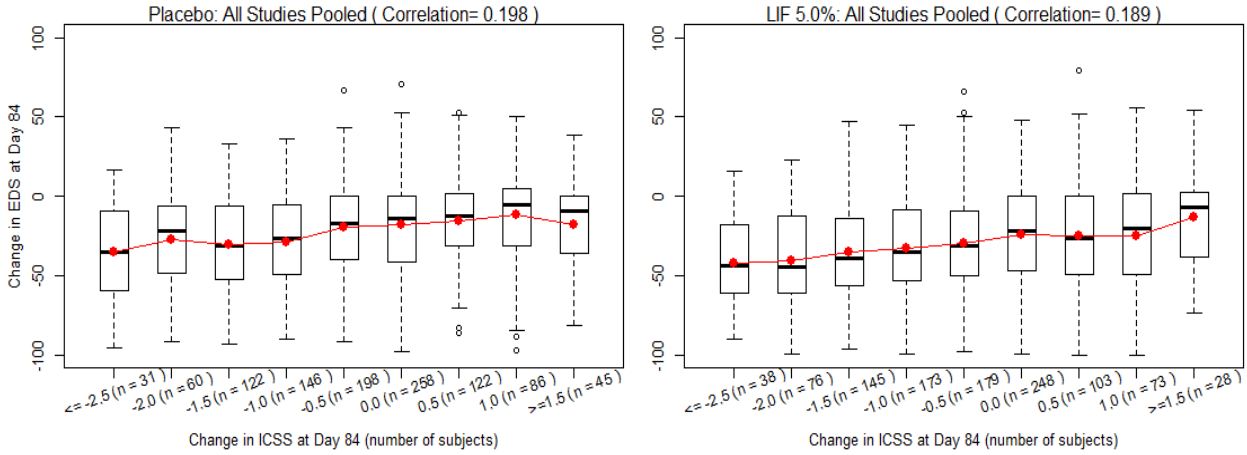
b) Relationship between ICSS and EDS at Day 84 (After treatment was received for 84 days)

The relationship between ICSS and EDS after treatment was received for 84 days was also explored in this section.

Reference ID: 3938302

In Figure 13 below, the distributions of the change in EDS from baseline at Day 84 were shown for each study arms by the unique values of the change in ICSS from baseline at Day 84. The relationship between ICSS and EDS after treatment was received for 84 days was not strong in each study arms - subjects that showed large improvement in ICSS at Day 84 (left side of x-axis) showed slightly better improvement in EDS (bottom of y-axis) compared to those who showed small or no improvement in ICSS.

Figure 13: Distribution of the Change in EDS at Day 84 by the Change in ICSS at Day 84 (ITT Population; LOCF)



Note: Dots and lines in red were for the mean change in EDS from baseline at Day 84

To further assess the relationship between the sign and symptom of DED, the proportion of subjects who achieved ≥50%, 25-50%, 0-25%, or ≤ 0% reduction in EDS at Day 84 was summarized by those who achieved ≥25%, 0-25%, and ≤ 0% reduction in ICSS at Day 84. Note that the ≤ 0% category in both cases represents no reductions or worsening.

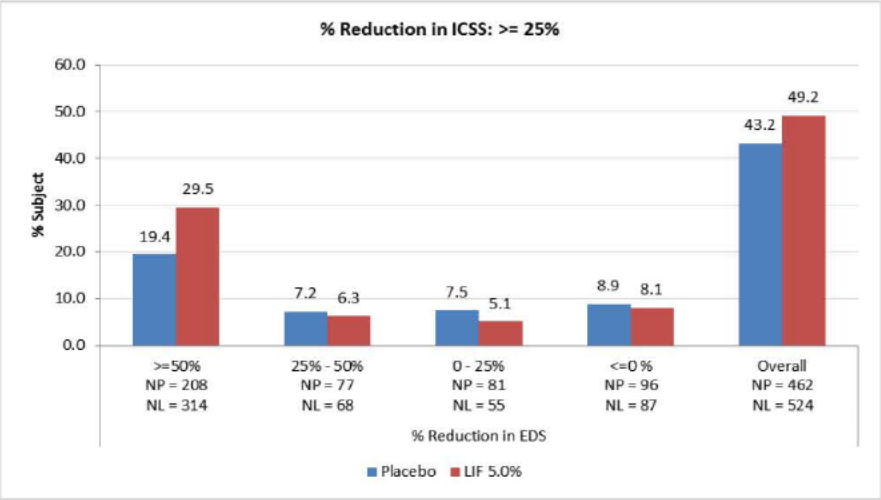
The summary results are shown in Figure 14 below, and the following observations were made based on the results:

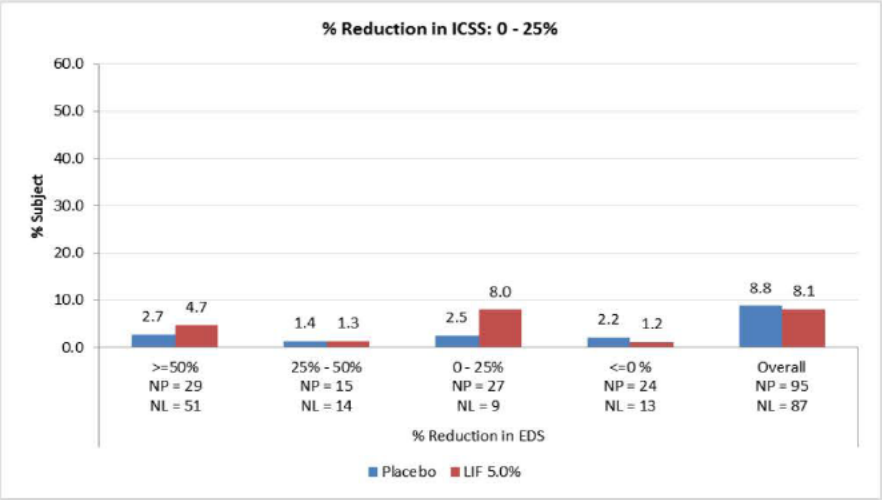
- About 49% of LIF 5% treated subjects and 43% of placebo treated subjects in the pooled data showed at least 25% reduction in ICSS from baseline at Day 84, and a large proportion of these subjects also showed at least 50% reduction in EDS; that is, about 30% of the overall LIF 5% treated subjects and 19% of the overall placebo treated subjects. (See top left panel of Figure 14). Furthermore,
- About 43% of LIF 5% treated subjects and 48% of placebo treated subjects in the pooled data did not show reduction in ICSS at Day 84 (See bottom left panel of Figure 14), but a large proportion of these subjects showed:
  a) At least 50% reduction in EDS at Day 84 (i.e., about 20% of the overall LIF 5% treated subjects and 17% of the overall placebo treated subjects) or
  b) No reduction in EDS at Day 84 (i.e., about 11% of the overall LIF 5% treated subjects and 17% of the overall placebo treated subjects).

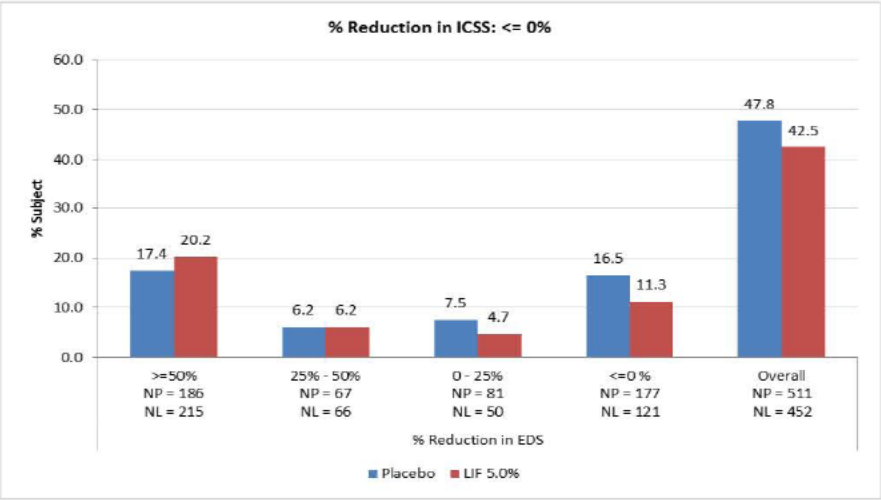
In summary, the clinical data summarized in the original and the current NDA submssions did not show a clear relationship between the clinical sign (as measured in ICSS) and the clinical symptom (as measured in EDS) of dry eye condition.

Reference ID: 3938302

Figure 14: Proportion of Subjects by Percent Reduction in ICSS and in EDS Categories at Day 84.
(ITT Population; LOCF)







Note Percentage was calculated based the total number of subjects in each study arm (N = 1068 for Placebo and N = 1063 for LIF 5.0%)

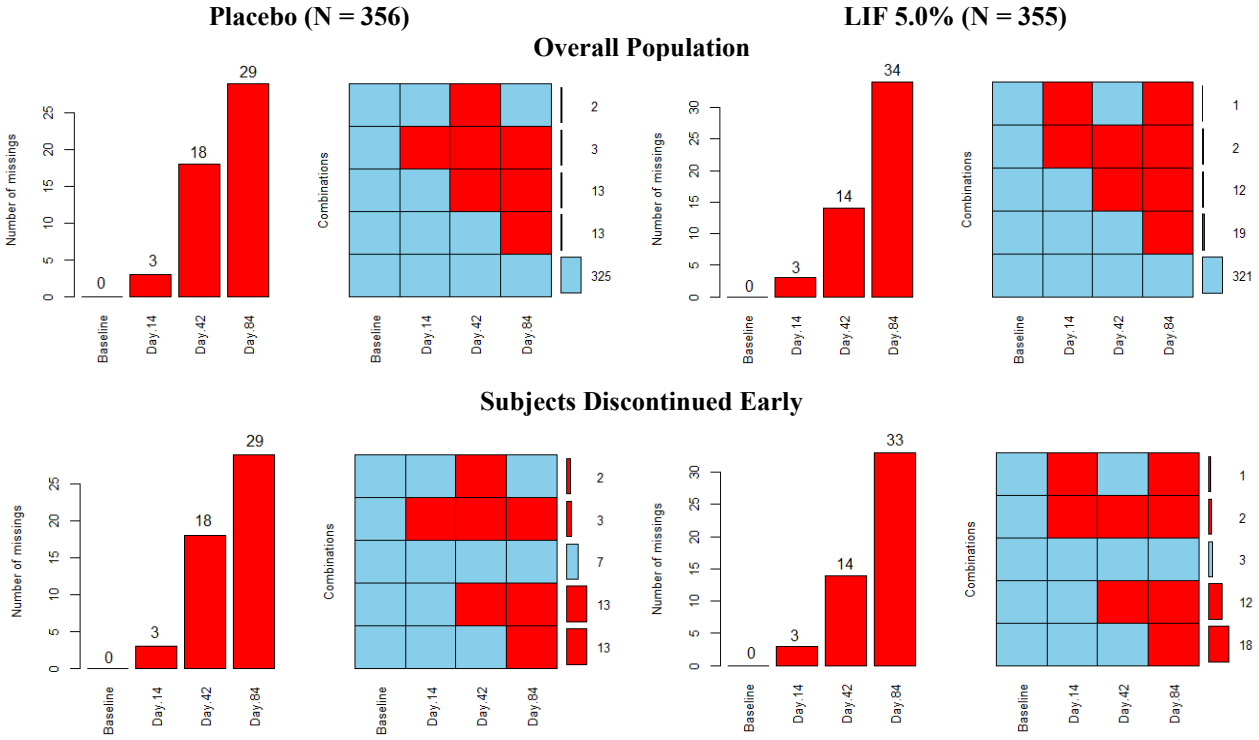
Reference ID: 3938302

3.2.4.4 Sensitivity Analysis

In the OPUS-3 study, a total of 74 (10%) subjects discontinued from the study before Day 84. The discontinuation rates between the study arms were comparable (about 10% each). Adverse event was the most common reason for discontinuation in the treatment arm (about 6.2% versus 2.5% in placebo).

The number of subjects in each study arms with available data (blue color) and missing data (red color) at each study visit are shown in Figure 15 below and in Table 3. Note that about 34 subjects (9.3%) in the LIF 5.0% treated group and 29 subjects (8.1%) in the Placebo group had missing data at Day 84, and the majority of the missing values at Day 84 were mainly due to early dropout (33 of 34 subjects in the LIF 5.0% group and 26 of 29 subjects in the placebo group).

Figure 15: Missing Data Pattern for the Overall Population and for Subjects Discontinued Early



Note: Subjects with missing data at a given represented by red color

To assess the impact of missing data due to early drop-out or missed visit on the primary efficacy analyses results, several sensitivity analyses were performed under different missing data handling approaches.

- ANCOVA model using observed data (without missing data imputation) and using worst observation carried forward (WOCF) for imputing missing data, and
- A mixed model repeated measure analysis (MMRM) using observed data and

In each case, the robustness of the primary efficacy results was evaluated under the different missing data handling methods. Note that the same sensitivity analyses methods were used in the statistical review for the original NDA (See Appendix 6.2).

Reference ID: 3938302

In Table 9 below, the sensitivity analyses results for the sign and symptom efficacy endpoints are shown for the OPUS-3 study.

Table 9: Mean Change in ICSS and EDS at Day 84: Sensitivity Analyses Results (ITT Population)

		Placebo		LIF 5.0%		Difference in LSM (95% CI)	P-value
		N	LSM (SE)	N	LSM (SE)		
ICSS	Observed Cases	327	-0.64 (0.050)	322	-0.83 (0.050)	-0.19 (-0.33, -0.05)	0.0082
	MMRM [1]	327	-0.57 (0.058)	322	-0.74 (0.060)	-0.18 (-0.32, -0.04)	0.0112
	WOCF	356	-0.58 (0.048)	355	-0.74 (0.048)	-0.16 (-0.29, -0.02)	0.0216
EDS	Observed Cases	327	-31.9 (1.50)	321	-39.8 (1.51)	-7.9 (-12.1, -3.76)	0.0002
	MMRM [1]	327	-31.6 (1.73)	321	-39.1 (1.74)	-7.5 (-11.6, -3.36)	0.0004
	WOCF	356	-28.9 (1.50)	355	-35.8 (1.50)	-6.9 (-11.0, -2.73)	0.0012

[1] The MMRM model used an unstructured covariance matrix to account for correlated measurements within patient and included the fixed effects for treatment, visit, actual baseline values, strata, and the interaction terms of treatment by visit.
LSM: Least Square Mean; SE: Standard Error

The sensitivity analyses results for both ICSS and EDS at Day 84 were consistent with the primary efficacy analysis approach that used LOCF method for imputing missing data.

Reference ID: 3938302

3.3 Safety Evaluation

All the studies included in the original NDA submission (Phase 2, OPUS-1, and OPUS-2) and in the current NDA re-submission (OPUS-3) had similar safety profiles.

A high level safety summary for the Phase 2, OPUS-1, OPUS-2, and SONATA studies was provided in the statistical review for the original NDA submission (See Appendix 6.2).

A high level safety summary for the OPUS-3 study was as follows; see the FDA clinical review for a comprehensive safety evaluation of the drug product.

- The study arms in OPUS-3 study had the same treatment duration on average: 79.8 days (SD = 17.4) in the placebo arm and 79.3 days (SD = 18.3) in the treatment arm.
- More subjects in the treatment arm (40%) reported ocular treatment emergent adverse events (TEAEs) compared to in the placebo arm (18%).
- There was no ocular serious TEAEs or TEAEs resulting in death reported in the study.
- The most frequently (≥5%) reported ocular TEAEs in both study arms were instillation site complaints with a much higher rate reported in the treatment arm:
  - Instillation site irritation: 18% in the treatment arm versus 3% in the placebo and
  - Instillation site reaction: 13% in the treatment arm versus 5% in the placebo.
- A total of 23 subjects were discontinued from treatment due to an ocular TEAE (placebo: 6 subjects; lifitegrast: 17 subjects). The most common ocular TEAEs that led to treatment discontinuation were instillation site reaction (placebo: 2 subjects; lifitegrast: 5 subjects) and instillation site irritation (placebo: 0 subjects; lifitegrast: 4 subjects).
- The most frequently reported non-ocular TEAE was dysgeusia, a higher percentage of subjects in the treatment arm reported dysguesia (13%) compared to in the placebo arm (0.3%).

Reference ID: 3938302

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

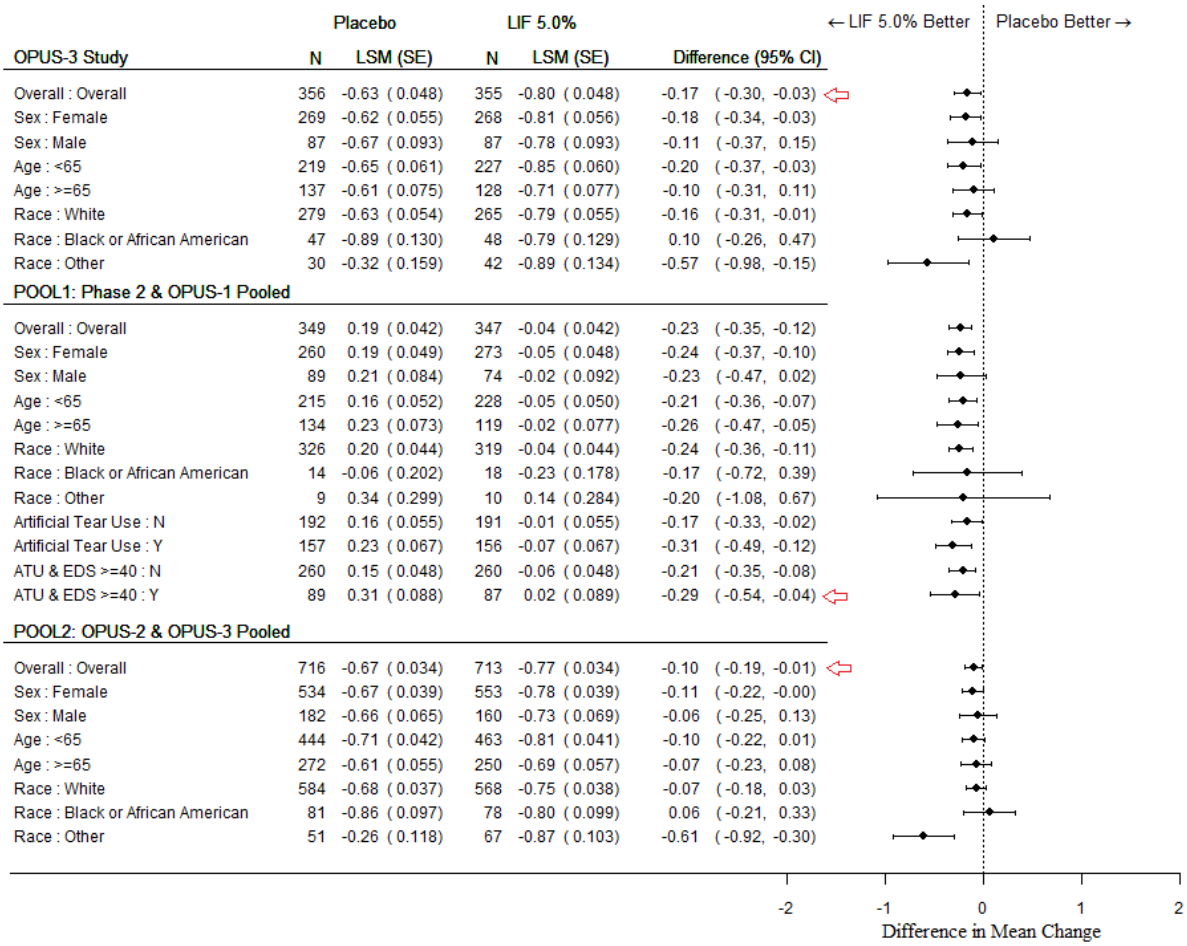
In this sections, the mean change in ICSS and in EDS from baseline at Day 84 were analyzed by the subgroup of age, sex, race, history of artificial tear use (ATU), and by history of ATU and baseline EDS ≥ 40. The subgroup analyses were performed in a manner similar to the primary analysis approach and were presented here for the OPUS-3 data, the pooled Phase 2 and OPUS-1 data (POOL1), and the pooled OPUS-2 and OPUS-3 data (POOL2). Similar subgroup analyses for the individual Phase 2, OPUS-1, and OPUS-2 studies were performed in the original NDA statistical review (See Appendix 6.2).

The summary of the mean changes in ICSS and the mean changes in EDS from baseline at Day 84 were shown by the levels of the subgroup variables in Figure 16 and Figure 17, respectively.

Overall, the efficacy results within the levels of each of the subgroup variables were consistent with those seen in the overall population. In some subgroups there were only small number of subjects, and the results for these subgroups may not be indicative of the overall treatment effects.

Figure 16: Mean Change (±SE) in ICSS from Baseline at Day 84 by Subgroup
(ITT Population, LOCF)

	Placebo		LIF 5.0%		
OPUS-3 Study	N	LSM (SE)	N	LSM (SE)	Difference (95% CI)
Overall : Overall	356	-0.63 (0.048)	355	-0.80 (0.048)	-0.17 (-0.30, -0.03)
Sex : Female	269	-0.62 (0.055)	268	-0.81 (0.056)	-0.18 (-0.34, -0.03)
Sex : Male	87	-0.67 (0.093)	87	-0.78 (0.093)	-0.11 (-0.37, 0.15)
Age : <65	219	-0.65 (0.061)	227	-0.85 (0.060)	-0.20 (-0.37, -0.03)
Age : >=65	137	-0.61 (0.075)	128	-0.71 (0.077)	-0.10 (-0.31, 0.11)
Race : White	279	-0.63 (0.054)	265	-0.79 (0.055)	-0.16 (-0.31, -0.01)
Race : Black or African American	47	-0.89 (0.130)	48	-0.79 (0.129)	0.10 (-0.26, 0.47)
Race : Other	30	-0.32 (0.159)	42	-0.89 (0.134)	-0.57 (-0.98, -0.15)
POOL1: Phase 2 & OPUS-1 Pooled					
Overall : Overall	349	0.19 (0.042)	347	-0.04 (0.042)	-0.23 (-0.35, -0.12)
Sex : Female	260	0.19 (0.049)	273	-0.05 (0.048)	-0.24 (-0.37, -0.10)
Sex : Male	89	0.21 (0.084)	74	-0.02 (0.092)	-0.23 (-0.47, 0.02)
Age : <65	215	0.16 (0.052)	228	-0.05 (0.050)	-0.21 (-0.36, -0.07)
Age : >=65	134	0.23 (0.073)	119	-0.02 (0.077)	-0.26 (-0.47, -0.05)
Race : White	326	0.20 (0.044)	319	-0.04 (0.044)	-0.24 (-0.36, -0.11)
Race : Black or African American	14	-0.06 (0.202)	18	-0.23 (0.178)	-0.17 (-0.72, 0.39)
Race : Other	9	0.34 (0.299)	10	0.14 (0.284)	-0.20 (-1.08, 0.67)
Artificial Tear Use : N	192	0.16 (0.055)	191	-0.01 (0.055)	-0.17 (-0.33, -0.02)
Artificial Tear Use : Y	157	0.23 (0.067)	156	-0.07 (0.067)	-0.31 (-0.49, -0.12)
ATU & EDS >=40 : N	260	0.15 (0.048)	260	-0.06 (0.048)	-0.21 (-0.35, -0.08)
ATU & EDS >=40 : Y	89	0.31 (0.088)	87	0.02 (0.089)	-0.29 (-0.54, -0.04)
POOL2: OPUS-2 & OPUS-3 Pooled					
Overall : Overall	716	-0.67 (0.034)	713	-0.77 (0.034)	-0.10 (-0.19, -0.01)
Sex : Female	534	-0.67 (0.039)	553	-0.78 (0.039)	-0.11 (-0.22, -0.00)
Sex : Male	182	-0.66 (0.065)	160	-0.73 (0.069)	-0.06 (-0.25, 0.13)
Age : <65	444	-0.71 (0.042)	463	-0.81 (0.041)	-0.10 (-0.22, 0.01)
Age : >=65	272	-0.61 (0.055)	250	-0.69 (0.057)	-0.07 (-0.23, 0.08)
Race : White	584	-0.68 (0.037)	568	-0.75 (0.038)	-0.07 (-0.18, 0.03)
Race : Black or African American	81	-0.86 (0.097)	78	-0.80 (0.099)	0.06 (-0.21, 0.33)
Race : Other	51	-0.26 (0.118)	67	-0.87 (0.103)	-0.61 (-0.92, -0.30)



LIF 5.0%: Lifitegrast Ophthalmic Solution 5.0%. LSM: Least Square Mean; SE: Standard Error; LSM (SE) was derived from ANCOVA model that adjusted for the baseline ICSS.

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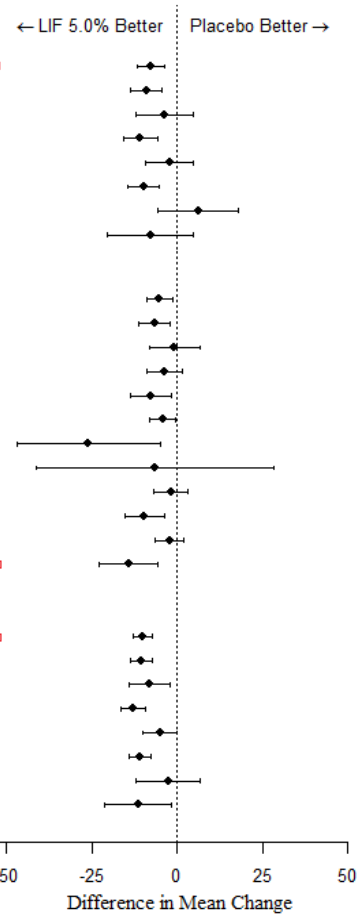
Figure 17: Mean Change (±SE) in EDS from Baseline at Day 84 by Subgroup
(ITT Population, LOCF)

OPUS-3 Study	Placebo N	Placebo LSM (SE)	LIF 5.0% N	LIF 5.0% LSM (SE)	Difference (95% CI)
Overall : Overall	356	-30.3 (1.45)	355	-37.8 (1.45)	-7.5 (-11.5, -3.5)
Sex : Female	269	-30.0 (1.65)	268	-38.9 (1.66)	-8.9 (-13.5, -4.3)
Sex : Male	87	-31.1 (3.04)	87	-34.8 (3.04)	-3.6 (-12.2, 4.9)
Age : <65	219	-29.0 (1.79)	227	-39.7 (1.76)	-10.7 (-15.6, -5.8)
Age : >=65	137	-32.4 (2.44)	128	-34.6 (2.53)	-2.2 (-9.1, 4.7)
Race : White	279	-28.8 (1.64)	265	-38.4 (1.68)	-9.7 (-14.3, -5.1)
Race : Black or African American	47	-40.5 (4.14)	48	-34.3 (4.09)	6.2 (-5.6, 18.0)
Race : Other	30	-29.6 (4.80)	42	-37.3 (4.05)	-7.7 (-20.3, 4.8)
POOL1: Phase 2 & OPUS-1 Pooled					
Overall : Overall	350	-10.4 (1.39)	346	-15.5 (1.40)	-5.1 (-9.0, -1.3)
Sex : Female	261	-10.1 (1.65)	272	-16.6 (1.61)	-6.6 (-11.1, -2.0)
Sex : Male	89	-11.0 (2.55)	74	-11.7 (2.80)	-0.7 (-8.2, 6.8)
Age : <65	216	-11.4 (1.83)	227	-15.0 (1.79)	-3.6 (-8.7, 1.4)
Age : >=65	134	-8.9 (2.10)	119	-16.4 (2.23)	-7.5 (-13.6, -1.5)
Race : White	327	-11.0 (1.41)	318	-15.3 (1.43)	-4.2 (-8.2, -0.3)
Race : Black or African American	14	2.1 (7.63)	18	-23.8 (6.73)	-25.9 (-46.8, -5.0)
Race : Other	9	-3.8 (11.72)	10	-10.1 (11.10)	-6.4 (-41.1, 28.4)
Artificial Tear Use : N	192	-11.2 (1.84)	190	-13.1 (1.85)	-1.8 (-7.0, 3.3)
Artificial Tear Use : Y	158	-9.1 (2.10)	156	-18.7 (2.12)	-9.5 (-15.4, -3.6)
ATU & EDS >=40 : N	261	-7.3 (1.53)	259	-9.5 (1.54)	-2.2 (-6.5, 2.0)
ATU & EDS >=40 : Y	89	-19.2 (3.09)	87	-33.4 (3.12)	-14.2 (-22.9, -5.5)
POOL2: OPUS-2 & OPUS-3 Pooled					
Overall : Overall	716	-26.6 (1.03)	713	-36.5 (1.03)	-9.9 (-12.8, -7.1)
Sex : Female	534	-26.8 (1.19)	553	-37.3 (1.17)	-10.5 (-13.7, -7.2)
Sex : Male	182	-25.8 (2.06)	160	-33.9 (2.20)	-8.1 (-14.1, -2.2)
Age : <65	444	-24.5 (1.28)	463	-37.4 (1.25)	-12.9 (-16.4, -9.4)
Age : >=65	272	-30.0 (1.72)	250	-34.9 (1.79)	-5.0 (-9.9, -0.1)
Race : White	584	-25.8 (1.13)	568	-36.8 (1.15)	-10.9 (-14.1, -7.8)
Race : Black or African American	81	-32.7 (3.27)	78	-35.3 (3.33)	-2.6 (-11.9, 6.7)
Race : Other	51	-24.7 (3.74)	67	-36.0 (3.27)	-11.4 (-21.2, -1.5)



Note that about 25% of the subjects in the Phase 2 and OPUS-1 pooled data (POOL1) had a history of ATU and with baseline EDS ≥ 40 similar to the overall population in the OPUS-2 and OPUS-3 studies.

The efficacy results (for both ICSS and EDS) in the subgroup in OPUS-1 and in the overall population in OPUS-2 and OPUS-3 were consistent (see red arrows) except that the treatment differences in the subgroup in OPUS-1 were numerically slightly larger than the overall population in OPUS-2 and OPUS-3.

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5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES

There are no major statistical issues identified in the current NDA submission. The following are minor issues identified during the review:

i) Data Issue

Randomization in the OPUS-3 study was stratified by baseline ICSS (≤1.5 or >1.5) and baseline EDS (< 60 or ≥ 60), and the following issues were identified during review of the data:

- A total of 36 subjects (16 in Placebo and 20 in LIF 5.0%) with baseline ICSS > 1.5 were incorrectly categorized as having baseline ICSS ≤ 1.5.
- Fifteen subjects (9 in Placebo and 6 in LIF 5.0%) with baseline ICSS ≤ 1.5 were incorrectly categorized as having baseline ICSS > 1.5.
- Fourteen subjects (6 in Placebo and 8 in LIF 5.0%) with baseline EDS ≥ 60 were incorrectly categorized as having baseline EDS < 60.
- Twelve subjects (7 in Placebo and 5 in LIF 5.0%) with baseline EDS < 60 were incorrectly classified as having baseline EDS ≥ 60.

The overall conclusion remained the same when all the efficacy data were re-analyzed using the correct stratification assignment.

ii) Analysis Issue: Primary Analysis Approach

The applicant primary efficacy analyses methods used in the Phase 2, OPUS-1, and OPUS-2 studies varied in the original NDA submission, but the OPUS-3 study used the same analysis approach as in OPUS-2. Due to the varied analyses methods used across the studies, ANCOVA model was used to analyze all the studies included in the original NDA and in the current NDA for ease of across study assessment.

Furthermore, all the studies included in the original NDA and the OPUS-3 study used LOCF for imputing missing data in the applicant primary efficacy analyses. The studies, however, differed in the use of the baseline values for imputing missing post-baseline values. In the OPUS-1 and OPUS-2 studies, the applicant analysis approach used baseline values for imputing missing post-baseline values but not in the Phase 2 and OPUS-3 studies. As a result, in the Phase 2 and OPUS- studies:

- Subjects with only baseline data were excluded in the applicant efficacy analysis of the ITT population with LOCF (Phase 2: seven subjects for both EDS and ICSS ; OPUS-3: five subjects for EDS and nine subjects for ICSS) and
- Subjects who had missing efficacy data at the first on-therapy visit (i.e., at Day 14) were not imputed in the applicant efficacy analysis of the ITT population with LOCF.

Because of the varied missing data handling approach across the studies and for ease of across study assessment, baseline values were used in the reviewer analysis approach for imputing missing post-baseline values in each study. We should note that the same conclusion was reached based on the applicant and the reviewer analysis approaches with the exception of minor numerical differences.

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5.2 Collective Evidence

In this NDA application, the applicant seeks approval of Xiidra (LIF 5.0%) for the treatment of the signs and symptoms of DED (b) (4). Efficacy and safety support for the proposed indication was based on a phase 2 dose-ranging and two phase 3 studies (OPUS-1 and OPUS-2) submitted in the original NDA and a phase 3 study (OPUS-3) submitted in the current NDA.

i) Efficacy Evidence for Clinical Symptom of DED

In OPUS-2 and OPUS-3 studies, LIF 5.0% treated group demonstrated statistically superior improvement in EDS early on and continued throughout the study compared to placebo treated group. At the end of the treatment period on Day 84, the improvement in EDS seen in the LIF 5.0% treated group was higher than placebo treated group by about 12 units in the OPUS-2 study, 8 units in the OPUS-3 study, 5 units in the OPUS-1 study, and 7 units in the Phase 2 study.

Therefore, based on the primary efficacy evidences for symptom seen in the OPUS-2 and OPUS-3 studies and the supportive evidences seen in the Phase 2 and OPUS-1 studies; treatment with LIF 5.0% demonstrated evidence of efficacy in improving the clinical symptoms of dry eye disease (as measured in EDS) compared to placebo.

ii) Efficacy Evidence for Clinical Sign of DED

In the Phase 2 and OPUS-1 studies, placebo treated group showed worsening in ICSS at Day 84 whereas LIF 5.0% treated group in these studies showed no change from baseline on average. In both studies, the mean reduction in ICSS at Day 84 in the LIF 5.0% treated group was higher than in the placebo treated group by about a quarter unit, and this difference was statistically superior in the OPUS-1 study and was marginally significant in the Phase 2 study.

In the OPUS-2 and OPUS-3 studies, both placebo and LIF 5.0% treated groups demonstrated at least half unit improvement early on (at Day 14) and continued improving throughout the study. At the end of the treatment period on Day 84; both groups in OPUS-2 showed equal amount of improvement (about 0.7 units) from baseline on average, and LIF 5.0% treated group in OPUS-3 showed about 0.8 unit improvement while placebo showed about 0.6 unit improvement.

Therefore, based on the primary efficacy evidences for clinical sign in the Phase 2 and OPUS-1 studies, and the supportive evidence in the OPUS-2 and OPUS-3 studies, treatment with LIF 5.0% demonstrated better efficacy benefit in maintaining or improving the clinical signs of dry eye disease (as measured in ICSS) compared to placebo.

iii) Safety Assessment

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

5.3 Conclusion and Recommendation

Based on my review of the three studies in the original NDA submission (Phase 2, OPUS-1, and OPUS-2) and the additional efficacy data from the OPUS-3 study, lifitegrast ophthalmic solution 5.0% demonstrated evidence of efficacy for the treatment of signs (as measured in ICSS) and in symptoms (as measured in EDS) of dry eye disease (b) (4).

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5.4 Labeling Recommendation

In the Clinical Studies Section 14, the applicant proposed to present the efficacy results for clinical sign (as measured in ICSS) from the Phase 2 (Study 1) and OPUS-1 (Study 2) studies and the efficacy results for clinical symptom (as measured in EDS) from the OPUS-2 (Study 3) and OPUS-3 (Study 4) studies.

However, we recommended that the efficacy results from all the studies be presented in the clinical study section in order to provide the prescribing physicians and patients a complete picture of the drug product efficacy results across the studies. Accordingly, we recommended the following figures to be included in the Clinical Study Section 14:

Mock Figure 1: Mean Change (SD) from Baseline Treatment Difference (Xiidra – Vehicle) in Eye Dryness Score in 12-Week Studies in Patients with Dry Eye Disease

Study 1

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

Study 2

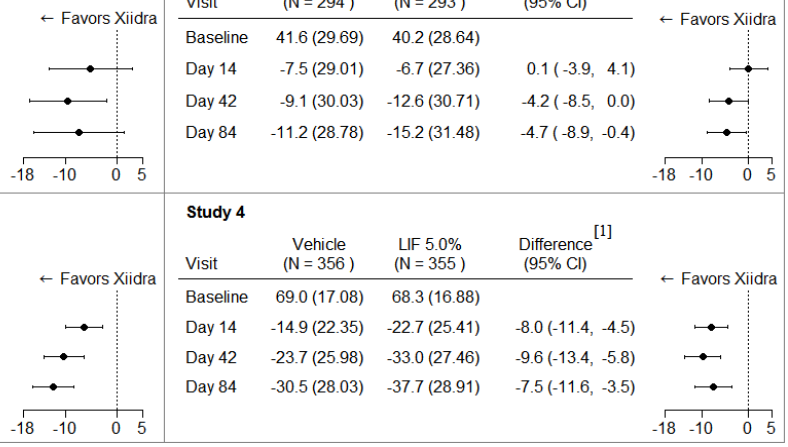
Visit	Vehicle (N = 294)	LIF 5.0% (N = 293)	Difference[1] (95% CI)
Baseline	41.6 (29.69)	40.2 (28.64)	
Day 14	-7.5 (29.01)	-6.7 (27.36)	0.1 (-3.9, 4.1)
Day 42	-9.1 (30.03)	-12.6 (30.71)	-4.2 (-8.5, 0.0)
Day 84	-11.2 (28.78)	-15.2 (31.48)	-4.7 (-8.9, -0.4)

Study 3

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

Study 4

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



[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated subjects were included in the analysis and missing data were imputed using last-available data. In Study 1, one LIF 5.0% treated subject who did not have a baseline value was excluded from analysis

Mock Figure 2: Mean Change (SD) from Baseline and Treatment Difference (Xiidra – Vehicle) in Inferior Corneal Staining Score in 12-Week Studies in Patients with Dry Eye Disease.

Study 1

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

Study 2

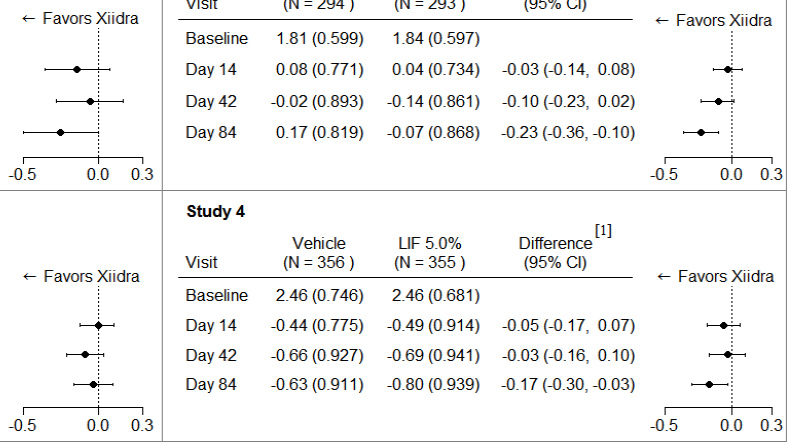
Visit	Vehicle (N = 294)	LIF 5.0% (N = 293)	Difference[1] (95% CI)
Baseline	1.81 (0.599)	1.84 (0.597)	
Day 14	0.08 (0.771)	0.04 (0.734)	-0.03 (-0.14, 0.08)
Day 42	-0.02 (0.893)	-0.14 (0.861)	-0.10 (-0.23, 0.02)
Day 84	0.17 (0.819)	-0.07 (0.868)	-0.23 (-0.36, -0.10)

Study 3

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

Study 4

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



[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated subjects were included in the analysis and missing data were imputed using last-available data. In Study 2, one Placebo treated subject who did not have a study eye designated was excluded from analysis.

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6. APPENDIX

6.1 SUMMARY OF IMPROVEMENT IN ICSS AND IN EDS FROM BASELINE AT DAY 84

Table 10: Proportion of Subjects with ≥ 1 unit and ≥ 2 units Improvement in ICSS from Baseline at Day 84
(ITT Population; LOCF)

	At least one unit improvement			At least two units improvement		
	Placebo n/N (%)	LIF 5.0% n/N (%)	% Difference [1] (95% CI)	Placebo n/N (%)	LIF 5.0% n/N (%)	% Difference [1] (95% CI)
Phase 2	5/ 58 (9)	11/ 58 (19)	10 (-4, 25)	0/ 58 (0)	1/ 58 (2)	2 (-2, 6)
OPUS-1	41/294 (14)	65/293 (22)	8 (1, 15)	3/294 (1)	8/293 (3)	2 (-1, 4)
OPUS-2	163/360 (45)	177/358 (49)	4 (-4, 13)	53/360 (15)	44/358 (12)	-2 (-8, 3)
OPUS-3	150/356 (42)	179/355 (50)	8 (-0, 16)	35/356 (10)	61/355 (17)	7 (2, 13)

[1] Difference with confidence interval (CI) based on using Cochran-Mantel-Haenszel (CMH) weighting scheme adjusted by study specific stratification factor

Table 11: Proportion of Subjects with ≥10 and ≥20 units Improvement in EDS from Baseline at Day 84
(ITT Population; LOCF)

	At least 10 units improvement			At least 20 units improvement		
	Placebo n/N (%)	LIF 5.0% n/N (%)	% Difference [1] (95% CI)	Placebo n/N (%)	LIF 5.0% n/N (%)	% Difference [1] (95% CI)
Phase 2	25/ 58 (43)	25/ 57 (44)	0 (-21, 21)	14/ 58 (24)	16/ 57 (28)	3 (-15, 22)
OPUS-1	132/295 (45)	144/293 (49)	4 (-5, 14)	99/295 (34)	115/293 (39)	6 (-3, 15)
OPUS-2	225/360 (63)	286/358 (80)	17 (10, 25)	184/360 (51)	253/358 (71)	20 (12, 28)
OPUS-3	257/356 (72)	288/355 (81)	9 (2, 16)	215/356 (60)	265/355 (75)	14 (6, 22)

[1] Difference with confidence interval (CI) based on using Cochran-Mantel-Haenszel (CMH) weighting scheme adjusted by study specific stratification factor

6.2 STATISTICAL REVIEW FOR ORIGINAL NDA

The statistical review for the original NDA which included the Phase 2, OPUS-1 and OPUS-2 studies is attached below.

Reference ID: 3938302

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208073
Drug Name:	Xiidra (Lifitegrast Ophthalmic Solution, 5.0 %)
Indication(s):	For the treatment of signs and symptoms of dry eye disease (b) (4)
Applicant:	SHIRE DEVELOPMENT LLC
Date(s):	Stamp Date: February 25, 2015
	PDUFA Date: October 25, 2015
	Review Date: July 20, 2015
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Solomon Chefo, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D., Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Rhea Lloyd, MD, Medical Officer
	William Boyd, MD, Team Leader
Project Manager:	Christina Marshall

Keywords: Clinical Studies, ANCOVA, Dry Eye Disease

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1 EXECUTIVE SUMMARY

The applicant seeks approval of Lifitegrast Ophthalmic Solution (XIIDRA™) 5.0% administered to the ocular surface as a single drop twice daily for the treatment of signs and symptoms of dry eye disease (DED) (b) (4).

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

The three studies were multicenter, randomized, double-masked, placebo-controlled studies conducted in adult subjects with DED and were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild-to-moderate symptom and the OPUS-2 study enrolled subjects with moderate-to-sever symptom. Each study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) - two weeks open label placebo run-in screening period (Day -14 to Day 0) followed by 12 weeks treatment period (Day 0 to 84). Eligible subjects in the Phase 2 study were randomized in a 1:1:1:1 ratio to receive either lifitegrast solution (LIF 0.1%, 1.0%, or 5.0% doses) or Placebo, and in OPUS-1 and OPUS-2 were randomized in a 1:1 ratio to receive either LIF 5.0% or Placebo as a single drop twice daily in each eye for 12 weeks (84 Days).

In each study, efficacy for the treatment of DED was assessed using clinical signs (objective) and symptoms (subjective) of dry eye. The primary sign efficacy endpoint in each study was based on the inferior corneal staining score (ICSS): ICSS at Day 84 was the primary sign endpoint in the Phase 2 study and the change in ICSS from baseline at Day 84 was the co-primary sign endpoint in the OPUS-1 and OPUS-2 studies. The OPUS-1 and OPUS-2 studies also included co-primary efficacy endpoint for symptom, and the two studies differed in this endpoint: the co-primary symptom endpoint in the OPUS-1 study was the change from baseline in the visual-related function subscale of the Ocular Surface Disease Index (VR_OSDI) score at Day 84, and in the OPUS-2 study was the change from baseline in the eye dryness score (EDS) of the visual analogue scale (VAS) at Day 84.

In the applicant primary efficacy analysis, the primary efficacy sign and symptom variables at Day 84 were compared between the treatment groups using the intent-to-treat (ITT) population with last observation carried forward (LOCF) method for imputing missing data: in the Phase 2 study, analysis of covariance (ANCOVA) model was used to compare the mean ICSS at Day 84 between the treatment groups; in OPUS-1 study, a two sample t-test was used to compare the mean changes in ICSS and in VR_OSDI score at Day 84 between the treatment groups; in the OPUS-2 study, regression analysis (ANOVA) model was used to compare the mean changes in ICSS and in EDS at Day 84 between the treatment groups.

It should be noted that the primary sign endpoint in the Phase 2 study was the actual ICSS at Day 84 while in OPUS-1 and OPUS-2 was the change from baseline in ICSS at Day 84; furthermore, the applicant primary analysis in the Phase 2 study adjusted for the baseline values while the primary analyses in OPUS-1 and OPUS-2 did not adjust for the baseline values. Therefore, for ease of across study assessment, ANCOVA model using the change from baseline value as response variable and the baseline value as covariate was performed by the statistical reviewer for all studies in this review. Note that using the actual or the change from baseline value as a response variable in the ANCOVA model provides the same results for treatment comparison.

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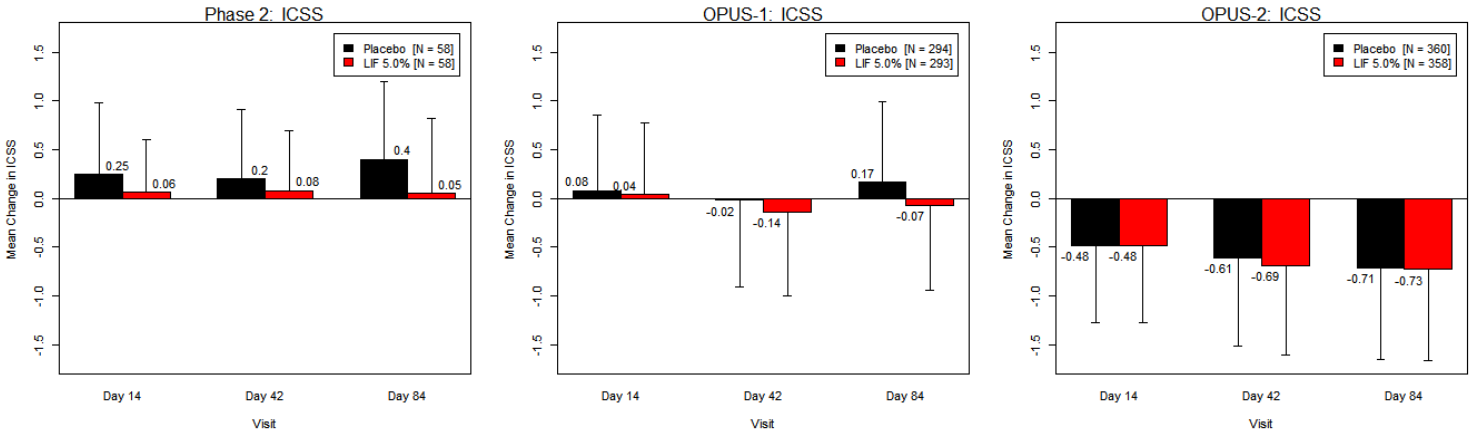
In each study, the majority of patients were Caucasian (≥85%), more than 70% were female, and the average age of patients was about 60 years. Approximately 40-50% of patients in the Phase 2 and in the OPUS-1 study had a recent history of artificial tear use (ATU) whereas all subjects in the OPUS-2 study were required to have a history of ATU. No marked difference was noted in the demographic characteristics between the treatment groups. The key sign and symptom baseline scores were also comparable between the treatment group in each study; however, by study design, the baseline mean ICSS and EDS scores in the OPUS-2 study (for both treatment groups) were much higher than in the Phase 2 and in the OPUS-1 studies (See Table 3).

i) Efficacy results for inferior corneal staining score (ICSS) at Day 84

The primary sign efficacy endpoint in each study was based on ICSS, and the efficacy results for the mean change in ICSS from baseline at each visit are shown in Figure 1 for each study.

Figure 1: Mean Change in ICSS from Baseline at each Visit (Standard Deviation)
(ITT Population, LOCF)



Source: Appendix Table 12

Statistical superiority in improving the clinical sign (as measured using ICSS) was demonstrated in only OPUS-1 study. In the Phase 2 and OPUS-2 studies, on the other hand, LIF 5.0% did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

In OPUS-1 study, LIF 5.0% treated group showed numerically larger mean reduction in ICSS from baseline at Day 84 compared with Placebo. The mean change in ICSS at Day 84 in the LIF 5.0% treated group was -0.07 (95% CI: -0.17, -0.04) and in the Placebo treated group was +0.17 (95% CI: 0.07, 0.26); the treatment difference (*LIF 5.0% minus Placebo*) was -0.23 (95% CI: -0.36, -0.09) and statistical significant difference was achieved in this study (p-value = 0.0007).

In the Phase 2 study, both LIF 5.0% and Placebo did not show mean reduction in ICSS from baseline throughout the study; however, a dose response in the mean change in ICSS was seen at Day 84 (See Figure 9). The mean change in ICSS at Day 84 in the LIF 5.0% treated group was +0.05 (95% CI: -0.16, 0.26) and in the Placebo treated group was +0.40 (95% CI: 0.18, 0.62); the treatment difference was -0.25 (95% CI: -0.51, 0.02) and not statistically significant (p-value = 0.0666). Though not statistically significant, the magnitude of treatment difference in this study (-0.25) was very close to what was seen in OPUS-1 study (-0.23); the non-statistical significant

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result in the Phase 2 study was likely due to smaller sample size compared with OPUS-1 study (note that the p-value in the Phase 2 study was close to 0.05).

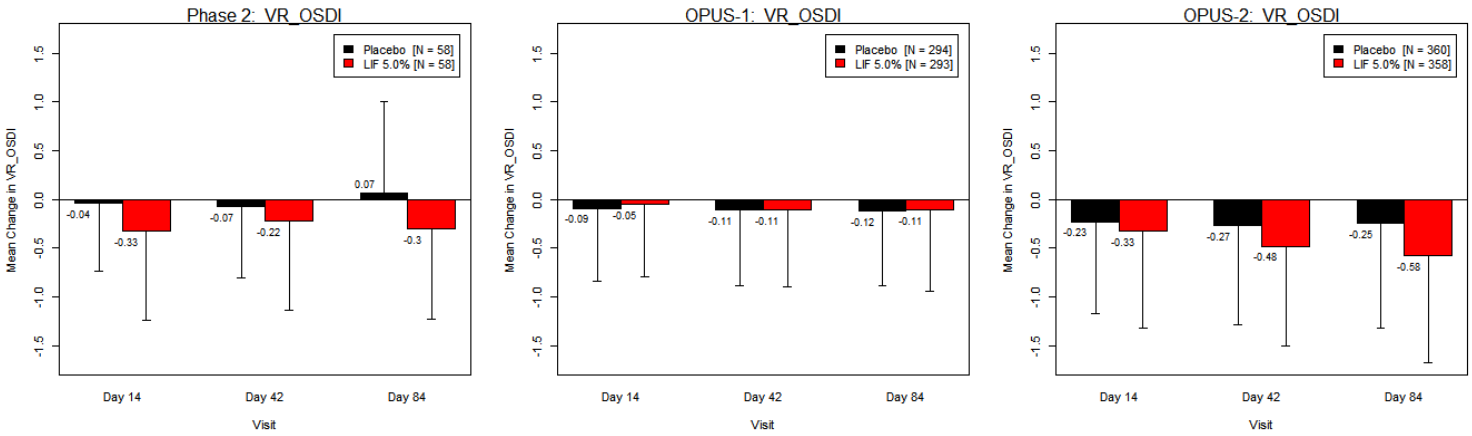
In the OPUS-2 study, both treatment groups showed numerically larger mean reductions in ICSS throughout the study compared with in the Phase 2 and OPUS-1 studies. The mean change in ICSS at Day 84 in the LIF 5.0% treated group in this study was -0.73 (95% CI: -0.83, -0.64) and in Placebo treated group was -0.71 (95% CI: -0.80, -0.61); the treatment difference was -0.03 (95% CI: -0.16, 0.10) and not statistically significant (p-value = 0.6122).

ii) Efficacy results for VR_OSDI score at Day 84

The change in VR_OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study and was supportive symptom endpoint in the Phase 2 and OPUS-2 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-2 studies were intended for descriptive use.

The efficacy results for the mean change in VR_OSDI score from baseline at each visit are shown in Figure 2 for each study.

Figure 2: Mean Change in VR_OSDI from Baseline at each Visit (Standard Deviation)
(ITT Population, LOCF)



Source: Appendix Table 13

Statistical superiority in improving clinical symptom (using VR_OSDI score) at Day 84 was not demonstrated in OPUS-1 study. In OPUS-2 study, LIF 5.0% treated subjects demonstrated a much larger improvement in VR_OSDI over Placebo and in the Phase 2 study showed a moderate improvement over Placebo. Additionally, a dose response improvement in VR_OSDI was seen at Day 84 (see Figure 11) in the Phase 2 study.

In OPUS-2 study, both treatment groups demonstrated larger mean reductions in VR_OSDI score from baseline throughout the study compared to in the Phase 2 and OPUS-1 studies. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.58 (95% CI: -0.70, -0.47) and in the Placebo treated group was -0.25 (95% CI: -0.36, -0.14); the treatment difference was -0.28 (95% CI: -0.41, -0.14; p-value < 0.0001).

In the Phase 2 study, LIF 5.0% treated group showed numerically slightly larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group. The mean change in VR_OSDI score from baseline at Day 84 in the LIF 5.0% treated group was

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-0.30 (95% CI: -0.56, -0.05) and in the Placebo treated group was +0.07 (95% CI: -0.18, 0.32); the treatment difference was -0.30 (95% CI: -0.63, 0.03; p-value = 0.0712).

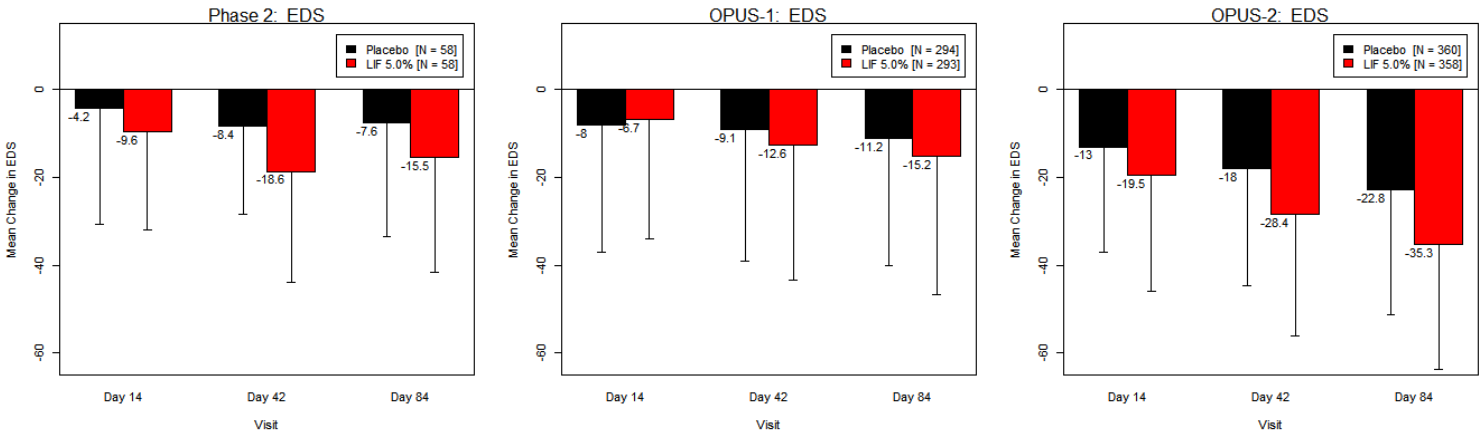
In the OPUS-1 study, both treatment groups showed small and comparable mean reductions in VR_OSDI score from baseline throughout the study. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.11 (95% CI: -0.20, -0.01) and in the Placebo treated group was -0.12 (95% CI: -0.21, -0.04); the treatment difference was -0.01 (95% CI: -0.12, 0.10) and not statistically significant (p-value = 0.8261).

iii) Efficacy results for Eye Dryness Score (EDS) at Day 84

The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2 and was supportive symptom endpoint in the Phase 2 and OPUS-1 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-1 studies were intended for descriptive use.

The efficacy results for the mean change in EDS from baseline at each visit are shown in Figure 3 for each study.

Figure 3: Mean Change in EDS from Baseline at each Visit (Standard Deviation)
(ITT Population, LOCF)



Source: Appendix Table 14

Statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated in OPUS-2 study. Both the Phase 2 and OPUS-1 studies showed numerically better improvement in EDS in the LIF 5.0% treated subjects over Placebo. Additionally, a dose response improvement of EDS was seen at Day 84 (see Figure 13) in the Phase 2 study.

In the OPUS-2 study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.3 (95% CI: -38.3, -32.3) and in the Placebo treated group was -22.8 (95% CI: -25.7, -19.8); the treatment difference was -12.3 (95% CI: -16.4, -8.3) and was strongly statistically significant (p-value < 0.0001).

In OPUS-1 study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.2 (95% CI: -18.8, -11.6) and in the Placebo treated group was -11.2 (95% CI: -14.5, -7.9); the treatment difference was -4.7 (95% CI: -8.9, -0.43; p-value = 0.0311). In this study, a much larger improvement in EDS form baseline at Day 84 was seen in a small subgroup of subjects with a recent history of ATU and with baseline EDS ≥40 (See Figure 31). In this subgroup, the

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mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.4 (95% CI: -43.4, -27.4) and in the Placebo treated group was -22.1 (95% CI: -29.8, -14.4); the treatment difference was -15.3 (95% CI: -25.9, -4.7). Note that the OPUS-2 study was designed based on the positive finding observed in this subgroup and the study used EDS as the primary symptom endpoint.

In the Phase 2 study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.5 (95% CI: -22.6, -8.3) and in the Placebo treated group was -7.6 (95% CI: -14.6, -0.5); the treatment difference was -7.6 (95% CI: -16.8, 1.5; p-value = 0.1021). Note that the confidence interval for the treatment difference did not exclude zero, and this was likely due to the smaller sample size compared to the OPUS-1 study.

Concluding Summary

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

Based on the totality of evidence, the statistical reviewer recommends for additional data from an adequate and well controlled study. The study, at a minimum, is expected to demonstrate statistical superiority of the test product over Placebo in improving a pre-defined clinical symptom. Furthermore, the test product in this study, at a minimum, is expected to show numerically better improvement in ICSS over Placebo or demonstrate similar level of reduction in ICSS seen in the OPUS-2 study.

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2 INTRODUCTION

2.1 OVERVIEW

In this NDA submission, the applicant seeks approval of Lifitegrast Ophthalmic Solution 5.0% (XIIDRA™) for the treatment of signs and symptoms of dry eye disease (DED).

DED is a multifactorial disease of the tears and ocular surface; it occurs when the eye does not produce tears properly, or when the tears are not of the correct consistency and evaporate too quickly. The disease for some people feels like there is a speck of sand in the eye, or stinging or burning that does not go away, and for others, the disease becomes a chronic condition that leads to blurred vision or vision loss if left untreated.

Dry eye is one of the most common of all eye conditions, primarily affecting adults 45 years and older. Many different things can cause dry eye, including environmental exposure, certain medications and medical conditions, eye surgery (such as laser correction surgery), and mainly staring at computer or video screens for too long without blinking.

Despite the prevalence of the disease, there are relatively few treatments available for DED. Current treatments include artificial tears, punctal plugs, and topical cyclosporine. In patients with aqueous tear deficiency, lubricating drops offer temporary relief and provide an important replacement of naturally produced tears. Punctal plug is another treatment option used to plug the drainage holes where tears drain from the eye into the nose.

Cyclosporine (RESTASIS®) is the only drug currently approved by the FDA to treat dry eye; however, it is only indicated for increasing tear production and is not indicated for the treatment of symptoms. Furthermore, it has a long onset of action (24 weeks), and is associated with reduced tolerance due to burning sensations.

The applicant indicated that treatments for DED with faster onset of action that are better tolerated and that can improve both the signs and symptom of the disease remains unmet medical need. To address this unmet medical need, the applicant developed Lifitegrast Ophthalmic Solution for the indication of treatment of signs and symptoms of DED.

2.1.1 Class and Indication

According to the applicant, Lifitegrast ophthalmic solution 5.0% 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 ophthalmic solution 5.0% is indicated for the treatment of the signs and symptoms of dry eye disease (b) (4).

2.1.2 History of Drug Development

The development of lifitegrast ophthalmic solution for the treatment of signs and symptoms of DED was submitted under initial IND (IND 77885) on 21 July 2008. Since then six Type B meetings were held with the Agency to discuss the lifitegrast development program.

The DED clinical development program included five completed and one ongoing randomized, double-masked, placebo-controlled clinical study:

- A Phase 1 dose-escalation study (SAR 1118-001) conducted in 28 healthy volunteers.

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- A Phase 2 dose-ranging study (1118-KCS-100, here after referred to as Phase 2) - a total of 230 subjects with DED were randomized to lifitegrast 0.1%, 1.0%, or 5.0% or placebo (1:1:1:1) and were treated twice daily dosing regimen for 12 weeks (84 days).
- The Phase 2 dry eye study evaluated the efficacy of lifitegrast 0.1%, 1.0%, and 5.0% twice daily. The applicant indicated that the greatest treatment effect was observed with lifitegrast 5.0% twice daily with an acceptable safety profile, and hence this dose regimen was chosen for the Phase 3 studies.
- Two Phase 3 studies (1118-KCS-200 and 1118-DRY-300, here after referred to as OPUS-1 and OPUS-2, respectively) - a total of 588 and 718 subjects were randomized to either lifitegrast 5.0% or placebo (1:1) in OPUS-1 and OPUS-2, respectively, and were treated twice daily dosing regimen for 12 weeks (84 days).
- One long-term multicenter, prospective, randomized, double-masked, placebo-controlled, parallel-arm safety study (1118-DRY-400; referred to as SONATA) - a total of 332 subjects were randomized to either lifitegrast 5.0% or placebo (2:1) and received a twice daily dosing regimen for 1 year (360 days) to compare the safety of lifitegrast 5.0%.
- One ongoing Phase 3, multicenter, randomized, double-masked, placebo-controlled, 12-week study designed to evaluate the safety and efficacy of lifitegrast (OPUS-3). The ongoing study was initiated in November 2014 and the applicant indicated that data from this study will be reported separately.

The study protocols for these studies were initially issued on 05 August 2011 for the Phase 2 study, on 01 June 2009 for OPUS-1 study, and on 05 August 2011 for OPUS-2 study. Each study protocol was subsequently amended one time (Phase 2 study protocol on 01 June 2009, OPUS-1 study protocol on 27 May 2011, and OPUS-2 study protocol on 06 November 2012).

The Phase 2 dose-ranging study and the two Phase 3 studies, OPUS-1 and OPUS-2, were conducted to generate the pivotal efficacy and safety support for the proposed indication.

2.1.3 Specific Studies Reviewed

The submission contains four completed study results: (i) a Phase 2 dose-ranging study and two pivotal Phase 3 studies (OPUS-1 and OPUS-2) to provide efficacy and safety support and (ii) a Phase 3 study (SONATA) to provide safety support for the proposed indication.

The Phase 2, OPUS-1, and OPUS-2 studies were similar in design and all were conducted in the United States (US). Each study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) – two weeks open label placebo run-in screening period followed by 12 weeks treatment period. Treatment in each study was administered as a single drop twice daily (AM and PM) in each eye for 12 weeks. The three studies differed in the use of the controlled adverse environment [1] (CAE) model, proportions of subjects with a history of artificial tear use (ATU), efficacy endpoints, and study population (See more detail in Section 3.2.1).

In the Phase 2 study, a total of 230 subjects were enrolled from five sites all in the US. In this study, the CAE model was used at each scheduled study visits; key inclusion and exclusion criteria during the screening period was based on pre- and post-CAE evaluation while all efficacy analysis during the treatment period was based on the Pre-CAE evaluation. About 50%

[1] The CAE model is a regulated environmental setting aimed at exacerbating the signs and symptoms of dry eye for a fixed period of time.

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of enrolled subjects in this study had a history of ATU within six months prior to the screening visit on Day -14.

In OPUS-1 study, a total of 588 subjects were enrolled from 13 sites all in the US. In this study, CAE model was used during the screening period only (at Days -14 and 0), and key inclusion and exclusion criteria during the screening period was determined based on pre- and post-CAE evaluation. About 55% of enrolled subjects in this study had a history of ATU within six months prior to the screening visit on Day -14.

In OPUS-2 study, a total of 718 subjects were enrolled from 30 sites all in the US. In this study, CAE model was not used throughout the study, and all subjects enrolled in this study had a history of ATU within 30 days prior to the screening visit on Day -14. A brief summary of these pivotal studies are presented in Table 2.

Table 2: Summary of Pivotal Studies Reviewed

Study ID/ Study Type	**Study Design / Primary Study Objective**	**Dose, Route and Regimen/ # of Patients**	**Duration of Treatment / Primary endpoint**	**Study Population**
1118-KCS-100 (Phase 2) Efficacy and Safety	Phase 2, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by inferior corneal staining score (ICSS) measured without use of the CAE at Day 84	Lifitegrast (LIF) 0.1, 1.0, or 5.0% or placebo ophthalmic solution; single drop BID LIF 0.1% (N = 57) LIF 1.0% (N = 57) LIF 5.0% (N = 58) Placebo (N = 58) **Total (N= 230)**	12 Weeks (84 Days) The study included a primary sign efficacy endpoint: **Sign**: inferior corneal fluorescein staining score	• Subjects at least 18 years of age with dry eye disease. • had a history of ATU within six months prior to the screening visit on Day -14 • Subjects with mild-to-moderate symptom
1118-KCS-200 (OPUS-1) Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by change from baseline to Day 84 in ICSS and VR-OSDI and to evaluate safety and tolerability	Lifitegrast (LIF) 5.0% or Placebo ophthalmic solution; single drop BID LIF 5.0% (N = 293) Placebo (N = 295) **Total (N = 588)**	12 Weeks (84 Days) The study included co-primary efficacy endpoints: (i) **Sign**: inferior corneal fluorescein staining score and (ii) **Symptom**: visual-related function Ocular Surface Disease Index subscale (VR_OSDI) score	• Subjects at least 18 years of age with dry eye disease. • Had a history of ATU within six months prior to the screening visit on Day -14 • Subjects with mild-to-moderate symptom enrollment
1118-DRY-300 (OPUS-2) Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by change from baseline to Day 84 in ICSS and eye dryness score, and to evaluate safety and tolerability	Lifitegrast (LIF) 5.0% or Placebo ophthalmic solution; single drop BID LIF 5.0% (N = 358) Placebo (N = 360) **Total (N = 718)**	12 Weeks (84 Days) The study included co-primary efficacy endpoints: (i) **Sign**: inferior corneal fluorescein staining score and (ii) **Symptom**: Eye Dryness Score (EDS) [0–100 point visual analogue scale (VAS) in both eyes]	• Subjects at least 18 years of age with dry eye disease. • Had a history of ATU within 30 days prior to the screening visit on Day -14 • Subjects with moderate-to-severe symptom (EDS ≥40)

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Study ID/ Study Type	Study Design / Primary Study Objective	Dose, Route and Regimen/ # of Patients	Duration of Treatment / Primary endpoint	Study Population
1118-DRY-400 (SONATA) Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID LIF 5.0% (N = 221) Placebo (N = 111) **Total (N = 332)**	360 days (1 year) To evaluate safety as assessed by ocular and non-ocular adverse events	Subjects at least 18 years of age with dry eye disease.

Source: Applicant's Section 2.7.6 Synopsis of Individual Studies

2.2 DATA SOURCES

The data source for this review included the clinical study reports, the analysis and tabulation datasets, and the integrated summary of safety datasets. These were provided in electronic submission and are located at \\cdsesub1\evsprod\nda208073.

The data analyzed in this review were based on the Phase 2 dose-ranging study and the two Phase 3 studies submitted as the pivotal evidence to support the safety and efficacy of lifitegrast 5.0% ophthalmic solution. A high level safety summary was also provided based on the individual studies safety data and based on data from the single Phase 3 safety study (SONATA); a comprehensive safety evaluation is primarily covered in the FDA clinical review.

3 STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The NDA was provided in an electronic submission. It included, among other documents, the clinical study report for each study, the finalized protocols (including amendments) and the statistical analysis plans, both analysis and tabulation datasets, and case report forms for few selected subjects. The SAS codes used to perform the analyses and to create the analysis datasets were also provided.

There were no issues identified with respect to the quality and integrity of the submitted data. Although the submitted datasets were not fully CDISC compliant, the submission included certain elements of the CDISC standards. In addition, the '*Reviewer's Guide Document'* and the '*Define.pdf*' files included in the submission package provided sufficient detail to access and to easily work with the datasets.

Therefore, minimal efforts were needed and no additional support was required from other sources to process the data.

3.2 EVALUATION OF EFFICACY

3.2.1 Study Design and Endpoints

i) Study Design

Efficacy support for lifitegrast ophthalmic solution for the treatment of signs and symptoms of dry eye disease was based on three adequate and well controlled studies; a Phase 2 dose-ranging study (Phase 2) and two Phase 3 studies (OPUS-1 and OPUS-2).

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The three studies were multicenter, randomized, double-masked, placebo-controlled studies conducted in adult subjects with DED and were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild to moderate symptom while the OPUS-2 study enrolled subjects with moderate to severe symptoms. Additionally, CAE model was used in both the Phase 2 and OPUS-1 studies to determine key eligibility criteria while the OPUS-2 study was conducted without the use of the CAE model.

Each study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) - two weeks open label placebo run-in screening period (Day -14 to Day 0) followed by 12 weeks treatment period (Day 0 to 84). CAE model was introduced at all study visits in the Phase 2 study and at the screening visits (on Days -14 and 0) in the OPUS-1 study.

Treatment in each study was administered to the ocular surface as a single drop twice daily (AM and PM) in each eye for 12 weeks (84 Days).

The number subjects with dry eye that were enrolled in each study along with the respective study period are shown in table below:

Studies	**Number Enrolled/ Number of sites**	**Study Period** [1]
Phase 2	230 / 5	08/03/2009 to 02/18/2010
OPUS-1	588 / 13	08/29/2011 to 04/28/2012
OPUS-2	718 / 30	12/07/2012 to 10/01/2013

[1] First subject's consent to last subject's last protocol-defined assessment

The three studies shared some common inclusion criteria; the following were the common study inclusion criteria shared by these studies:

i) Male and Female subjects at least 18 years of age at the time of enrollment

ii) Subject with reported history of dry eye in both eyes

iii) Corneal fluorescein staining score of ≥2 in at least one eye at Days -14 and 0 (based on Pre-CAE score in the Phase 2 and OPUS-1 studies).

iv) Conjunctival redness score ≥1 in at least one eye at Days -14 and 0 (based on Pre-CAE score in the Phase 2 and OPUS-1 studies).

Furthermore, a positive response in at least one eye, defined as meeting all of the following criteria in the same eye was required for eligibility in the Phase 2 and OPUS-1 studies. In these studies, the worst eye that met these requirements was designated as the **study eye**.

- Change from pre-CAE to post-CAE in ICSS ≥ +1
- Ocular discomfort score (ODS) of ≥3 at two consecutive time points (or score of 4 at 2 consecutive time points if the pre-CAE score = 3 at the same visit)
- Schirmer Tear Test score (STT) without anesthesia of ≥1 mm and ≤10 mm.

In the OPUS-2 study, a positive response was defined as meeting ICSS ≥0.5 and STT score of ≥1 mm and ≤10 mm in the same eye at both Days -14 and 0; in this study, the worst eye (highest score) that met these requirements was designated as the **study eye**.

Recent artificial tear use for dry eye (within 30 days prior to Day -14) and EDS ≥40 at Days -14 and 0 were additional eligibility requirements unique in the OPUS-2 study.

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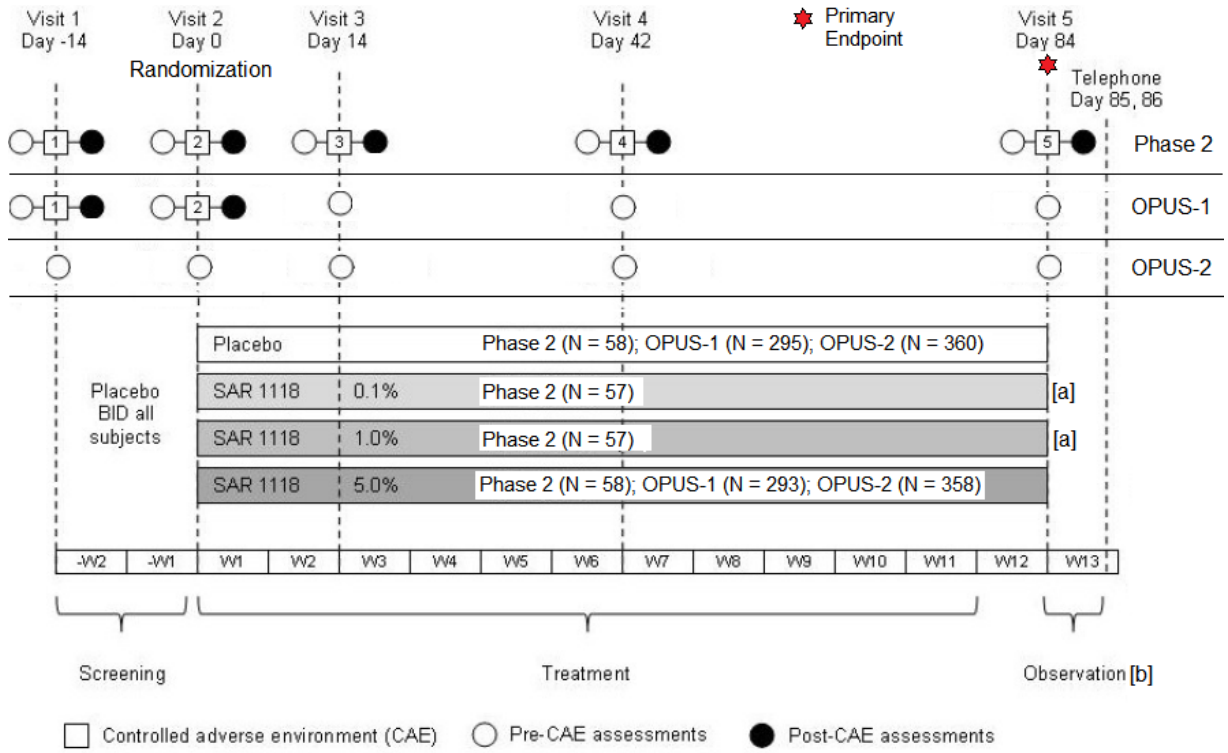
In the three studies, subjects that met all the study specific inclusion and none of the exclusion criteria entered the treatment period, and were randomized at Day 0 to receive either lifitegrast ophthalmic solution or placebo as a single eye drop twice daily in each eye for 84 days.

In the Phase 2 study, eligible subjects were randomized in a 1:1:1:1 ratio to receive either lifitegrast ophthalmic solution (LIF 0.1%, 1.0%, or 5.0%) or Placebo; and in OPUS-1 and OPUS-2, eligible subjects were randomized in a 1:1 ratio to receive either LIF 5.0% or Placebo.

Randomization in the OPUS-1 study was stratified by the Pre-CAE ICSS data in the study eye at Day 0 (≤ 1 versus >1) and by the prior use of artificial tears (Yes versus No). In OPUS-2 study, randomization was stratified by the ICSS data (≤ 1 versus >1) and EDS data (< 60 versus ≥60) in the study eye at Day 0.

In Figure 4 flowchart of each study designs is shown.

Figure 4: Flowchart of Study Design



[a] Specific to the Phase 2 study; [b] Not applicable in OPUS-2 study
Source: Figure 1 of Applicant's Clinical Overview

In each study, efficacy for the treatment of DED was assessed using clinical signs (objective) and symptoms (subjective) of dry eye. For both signs and symptoms of DED, efficacy data were collected at each study visit.

The key ocular sign parameters measured at all study visits included: corneal fluorescein score (inferior, central, and superior cornea), conjunctival lissamine score (nasal and temporal conjunctiva), and Schirmer Tear Test without anesthesia (mm/5min).

- The three regions of corneal fluorescein staining were scored in 0-4 scale with 0.5 increment (*0 = no staining, 1=Occasional, 2=Countable, 3=Uncountable but not confluent, and 4=Confluent*); the associated scores in OPUS-2 study were labeled slightly different (*0=no*

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staining, 1=few/rare punctate lesions, 2=discrete and countable lesions, 3=lesions too numerous to count but not coalescent, and 4=coalescent). The total corneal fluorescein score was derived as the sum of the three regions (0-12 points).

- The two regions of conjunctival lissamine green staining were also scored in 0-4 scale with 0.5 increments; the scores are labeled the same as the scores for corneal fluorescein staining.
- The schirmer tear test (without anesthesia) measured the tear production based on the length of wetting area (in mm/5 minutes) was recorded for each eye.

The key ocular symptom parameters included: ocular discomfort score (ODS), eye dryness score (EDS) of the 7-item visual analogue scale (VAS), and ocular surface disease index (OSDI).

- The ODS was measured in 0–4 point scale (0=no symptom; 4 = severe discomfort) relative to each eye based on subject-reported symptoms at each study visits
- The EDS was measured in 0-100 point scale (0 = no discomfort; 100=maximal discomfort) across both eyes based on subject-reported symptoms at each study visits.
- The OSDI measured in 0-100 scale (0=normal, 100=sever) was derived from 12 items subject-reported questionnaire recorded retrospectively with a 1-week recall period across both eyes. Each of the 12 items was graded on a 0-4 scale (0=none of the time, 4=all of the time, or N/A=not applicable) with the overall OSDI score converted to 0-100 scale.
- The OSDI has an overall score and three subscale scores (ocular symptoms, vision-related function, and environmental triggers). The visual related OSDI (VR_OSDI) subscale included 4 items (reading, driving at night, use of computer, and watching television) each measured in 0-4 scale; the overall VR_OSDI score was 0-4 mean composite score derived from these items.

ii) Study Endpoints

There are a number of clinically accepted sign and symptom efficacy endpoints for the treatment of signs and symptoms of DED, and applicants are generally expected to pre-specify such endpoints and get concurrence from the Agency beforehand. To make efficacy claim for dry eye indication, the test product was generally expected to demonstrate statistical superiority over placebo (vehicle) in improving a clinical sign and a clinical symptom of dry eye in at least two adequately and well controlled studies.

In this submission, the Phase 2 study included a single primary sign endpoint and the two pivotal Phase 3 studies included co-primary sign and symptom efficacy endpoints. The primary sign efficacy endpoint in each study was based on the inferior corneal staining score (ICSS); the OPUS-1 and OPUS-2 studies also included co-primary efficacy endpoint for symptom, and the two studies differed in this endpoint. Details are discussed below.

a) Phase 2 Study

The primary efficacy sign endpoint in the Phase 2 study was the mean ICSS in the study eye at Day 84 (without use of the CAE). In this study, no primary symptom endpoint was defined. However, a number of sign and symptom efficacy secondary endpoints were defined in the study protocol; the results for these endpoints were presented and discussed in the applicant clinical study report. All the secondary endpoints defined in the Phase 2 study protocol were intended to be exploratory in nature.

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b) Phase 3 Study: OPUS-1

i) *Co-primary Efficacy Endpoint:*

The study included co-primary sign and symptom endpoint:

- The co-primary sign endpoint was the mean change in ICSS from baseline at Day 84 in the designated study eye.
- The co-primary symptom endpoint was the mean change in VR_OSDI score from baseline at Day 84.

ii) Secondary Endpoints:

- The secondary sign endpoint was the mean in Schirmer Tear Test (STT; mm/5 minutes) score at Day 14 and at Day 84.
- The secondary symptom endpoint was the mean change in the Total OSDI score from baseline at Day 14 and at Day 84.

c) Phase 3 Study: OPUS-2

i) Co-primary Efficacy Endpoint:

The study included co-primary sign and symptom endpoint:

- The co-primary sign endpoint was the mean change in ICSS from baseline at Day 84 in the designated study eye.
- The co-primary symptom endpoint was the mean change in EDS from baseline at Day 84.

Note that the applicant symptom co-primary endpoint in this study, unlike in the OPUS-1 study, was based on EDS. In the OPUS-1 study, a positive finding in EDS was seen in the subgroup of subjects with a recent history of ATU and EDS ≥ 40. Consequently, in the OPUS-2 study, the applicant enrolled subjects with a recent history of ATU and with baseline EDS ≥ 40 and used EDS as a co-primary symptom endpoint in the study.

ii) Secondary Endpoints:

- The secondary sign endpoints were the mean change in total corneal fluorescein staining scores (Total CSS) and the mean change in nasal conjunctival lissamine green staining score (Nasal CLGSS) from baseline at Day 84 in the designated study eye.
- The secondary symptom endpoints were the mean change in eye discomfort score (EDisS) of the 7-item VAS and the mean change in ocular discomfort score (ODS) from baseline at Day 84.

Several supporting sign and symptom efficacy endpoints were defined in the Phase 2, OPUS-1, and OPUS-2 study protocols. We defer to the study specific clinical study reports for detail and summary of the supporting efficacy variables.

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3.2.2 Statistical Methodology

i) Phase 2 Study

The primary efficacy analysis in this study was a pairwise comparison between the three concentrations of lifitegrast ophthalmic solution (LIF 0.1%, 1.0%, and 5.0%) against Placebo in the primary sign efficacy endpoint of mean ICSS at Day 84.

The applicant primary efficacy analysis method used Analysis of Covariance (ANCOVA) methodology with ICSS at Day 84 as the response variable, and treatment, site, and the baseline ICSS as covariate. To compare the three lifitegrast doses against placebo in the mean ICSS, the applicant used Dunnett's test at two-sided alpha level of 5%.

The primary analysis was performed in the ITT population (defined below) using the last observation carried forward (LOCF) method for imputing missing data. All the secondary sign and symptom efficacy endpoints were analyzed in a similar manner as in the primary efficacy endpoint. Since the secondary endpoints were intended to be exploratory in nature, no formal correction for multiplicity was performed in this study.

As a supportive analysis, the applicant also used an unadjusted 2-sample t-test and a non-parametric Wilcoxon rank sum test. The applicant also analyzed the change from baseline at Day 84 using the same analysis approach.

Analysis Population

In this study, three analysis populations were defined. The intent-to-treat (ITT) population which included all randomized subjects, the per-protocol (PP) population excluded subjects with any major protocol deviations or with incomplete efficacy data from the analysis, and the safety analysis population (SAF) which included all randomized subjects who received at least 1 dose of study drug.

The ITT population was used for all efficacy analyses. The applicant also performed the primary efficacy analysis using the PP population.

ii) Phase 3: OPUS-1 Study

The primary efficacy analysis in this study compared LIF 5.0% against placebo in the co-primary sign endpoint of the mean change in ICCS from baseline at Day 84 and in the co-primary symptom endpoint of VR_OSDI score from baseline at Day 84.

The applicant's primary efficacy analysis for the mean change in ICSS and in VR_OSDI score from baseline at Day 84 was based on a two-sample t-test in the ITT population (defined below) with LOCF method for imputing missing data.

In the applicant analysis, all the secondary efficacy endpoints were analyzed in a similar manner as in the co-primary efficacy endpoints. Furthermore, the applicant proposed Simes modified Bonferroni procedure to control the Type I error rate across the secondary endpoints within an analysis population if both co-primary endpoints were significant.

Analysis Population

In this study as well, three analysis populations were defined. The ITT and SAF populations were identical and included all randomized subjects who received at least 1 dose of study drug.

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The PP population included all randomized subjects who completed the study with no major protocol violations.

iii) Phase 3: OPUS-2 Study

The primary efficacy analysis in this study compared LIF 5.0% against placebo in the co-primary sing endpoint of the mean change in ICCS from baseline at Day 84 and in the co-primary symptom efficacy endpoint of the mean change in EDS from baseline at Day 84.

The applicant's primary efficacy analysis for the mean change in ICSS and in EDS from baseline at Day 84 was performed using regression analysis (ANCOVA) model in the ITT population (defined below) with LOCF method for imputing missing data. The regression model included treatment, strata, and the interaction between treatment and strata.

In the applicant analysis, all the secondary efficacy endpoints were analyzed in a similar manner as in the co-primary efficacy endpoints. Furthermore, the applicant proposed Hochberg's procedure to control the type I error rate at 5% level across all secondary endpoints if both co-primary endpoints were significant.

Analysis Population

In this study, three analysis populations were defined. The randomized population which included all randomized subjects, and the ITT and SAF populations which included all randomized subjects who received at least 1 dose of study drug. Analyses conducted using the ITT population was based on treatment assigned and analyses conducted using the SAF population was based on treatment received.

In this study, per-protocol analysis population was not defined.

Reviewer's Analysis Approach:

i) Phase 2 Study

- The Phase 2 dose-ranging study was primarily designed to identify the most effective dose for the Phase 3 studies by comparing the mean ICSS score of LIF 0.1%, 1.0%, and 5.0% against Placebo. According to the applicant, the greatest treatment effect with an acceptable safety profile was observed with LIF 5.0%, and subsequently this dose regimen was studied in the two Phase 3 studies. Therefore, in this review, all efficacy analyses for the Phase 2 study compared LIF 5.0% dose group against Placebo without correction for multiple comparison.
- Even though only a single primary sign efficacy endpoint was defined in this study, data for a number of sign and symptom variables were also collected in this study including the co-primary symptom variables (EDS and VR_OSDI) and all the secondary sign and symptom variables defined for the OPUS-1 and OPUS-2 studies. Therefore, for the purpose of across study comparisons, all these variables were also analyzed for the Phase 2 study.
- We should note that, with the exception of the primary sign efficacy variable, all other sign and symptom efficacy variables analyzed for the phase 2 study were intended to be exploratory in nature.

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ii) OPUS-1 and OPUS-2 Studies

The applicant primary analysis approach in the OPUS-1 study used two-sample t-test to compare the treatment groups in the mean change in ICSS and in VR_OSDI score from baseline at Day 84. On the other hand, the applicant primary analyses in the OPUS-2 study used regression analysis (ANOVA model) to compare the treatment groups in the mean change in ICSS and in EDS from baseline at Day 84; in the ANOVA model, treatment, strata, and the interaction between treatment and strata were included as covariates. However, the applicant did not provide any justification for inclusion of the interaction term in the model, and there was also no reason to suspect an interaction effect (based on the applicant analysis method, the p-values for the interaction term was 0.7037 for ICSS and was 0.5782 for EDS).

Overall, the statistical reviewer noted that the three studies differed in the efficacy endpoint definition as well as in the primary efficacy analyses methods:

- The primary sign endpoint in the Phase 2 study was based on the actual ICSS at Day 84 whereas in the OPUS-1 and in the OPUS-2 studies was based on the change from baseline in ICSS at Day 84 and
- The applicant primary analysis in the Phase 2 study adjusted for the baseline values whereas the primary analyses in OPUS-1 and OPUS-2 did not adjust for the baseline values.

Therefore, for ease of across study assessment, the statistical reviewer primary analysis approach (for all the studies) used ANCOVA model based on the ITT population with LOCF for missing data. In the ANCOVA model, the change from baseline value at Day 84 was used as the response variable, and treatment, baseline value, and the study specific strata (specific for OPUS-1 and OPUS-2) were used as covariates. Note that using the actual value or the change from baseline value as a response variable in the ANCOVA model provides the same results for treatment comparison.

Based on the ANCOVA model, the difference in the mean change between the treatment groups was determined using the Least Square Means (LS Means). The default observed margin (OM) option in the LSMEANS statement of the PROC MIXED procedure in SAS was used to account for any imbalance in sample size and in the mean change values across strata.

As sensitivity analyses, the statistical reviewer also performed ANCOVA analysis using observed data (without missing data imputation) and unadjusted analysis using a two sample t-test and a non-parametric Wilcoxon rank sum test. Furthermore, a mixed model repeated measure (MMRM) analysis that accounted for correlated measurements was also performed using the observed data; the model used an unstructured covariance matrix to account for correlated measurements within patient and included the fixed effects for treatment, visit, actual baseline values, strata, and the interaction terms of treatment by visit. Treatment difference in the mean change from baseline at each visit was determined based on LS Means using the MMRM analysis.

Overall, the same efficacy conclusion was reached based on the applicant and the reviewer analyses methods. Furthermore, the sensitivity analyses and the MMRM analysis results were consistent with the primary efficacy analysis results.

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3.2.3 Patient Disposition, Demographics, and Baseline Disease Characteristics

Overall, 230, 588, and 718 patients were randomized in the Phase 2 (including all doses), OPUS-1, and OPUS-2 studies, respectively. Note that the results in Table 1 for patient disposition, in Table 2 for demographic summary, and in Table 3 for baseline disease characteristics only included LIF 5.0% for the Phase 2 study.

3.2.3.1 Patient Disposition

The summary of patient disposition and the primary reasons for study discontinuation during the 12-week treatment period in each study are shown in Table 1 below.

Table 1: Disposition of Patients and Reasons for Study Discontinuation
(All Randomized Subjects)

	Phase 2		**OPUS-1**		**OPUS-2**	
	Placebo (N = 58)	LIF 5.0% (N = 58)	Placebo (N = 295)	LIF 5.0% (N = 293)	Placebo (N = 360)	LIF 5.0% (N = 358)
Number of randomized subjects (ITT Population)	58 (100.0)	58 (100.0)	295 (100)	293 (100)	358 (100.0)	360 (100.0)
Safety Population	58 (100.0)	58 (100.0)	295 (100)	293 (100)	359 (99.7)	359 (100.3)
Per-protocol Population	44 (75.9)	46 (79.3)	265 (89.8)	246 (84.0)	NA	NA
Subjects who completed the study	48 (82.8)	48 (82.8)	284 (96.3)	281 (95.9)	348 (96.7)	321 (89.7)
Subjects discontinued from the study	10 (17.2)	10 (17.2)	11 (3.7)	12 (4.1)	12 (3.3)	37 (10.3)
Reason for withdrawal						
Adverse event	1 (1.7)	6 (10.3)	3 (1.0)	10 (3.4)	3 (0.8)	26 (7.3)
Lost to follow-up	2 (3.4)	1 (1.7)	2 (0.7)	0	0	2 (0.6)
Non-compliance	1 (1.7)	1 (1.7)	2 (0.7)	0	0	1 (0.3)
Pregnancy	0	0	1 (0.3)	0	0	0
Other	6 (10.3) [b]	2 (3.4) [a]	3 (1.0)	2 (0.7)	9 (2.5)	8 (2.2)

Source: Table 3 of Phase 2, OPUS-1, and OPUS-2 Clinical Study Reports. LIF 5.0% = lifitegrast 5.0% ophthalmic solution
[a] withdrew consent; [b] non-compliance due to disallowed medications

Of the 230 randomized subjects in the Phase 2 study, a total 29 (13%) subjects discontinued from the study; 10 (17%) subjects each discontinued from the LIF 5.0% and Placebo treated group before Week 12. Adverse event (AE) was the most common reason for discontinuation in the LIF 5.0% treated group (about 10% versus 2.0% in placebo) while non-compliance due to disallowed medications was the most common reason for discontinuation in the Placebo treated group (about 10%). One subjects in the placebo treated group discontinued due to non-ocular AE (due to sinus pressure and sinus infection) while all six subjects in the LIF 5.0% treated group discontinued due to ocular AE (*due to ocular infection, ocular pain, burning or stinging upon instillation of study drug, irritated eyelids, excess ocular tearing, or ocular redness*).

Of the 588 randomized subjects in OPUS-1 study; a total of 23 (4%) subjects discontinued from the study before Week 12; the discontinuation rates were comparable between the treatment groups. Adverse event was the most common reason for discontinuation in the LIF 5.0% treated group (3% versus 1% in Placebo). In the Placebo treated group, three subjects discontinued due to AE (*due to worsening of depression, eye pain, or increased central superficial punctate keratitis*). In the LIF 5.0% treated group, most of the discontinued subjects due to AE did so due to *burning, stinging, or blurred vision upon instillation of study drop*.

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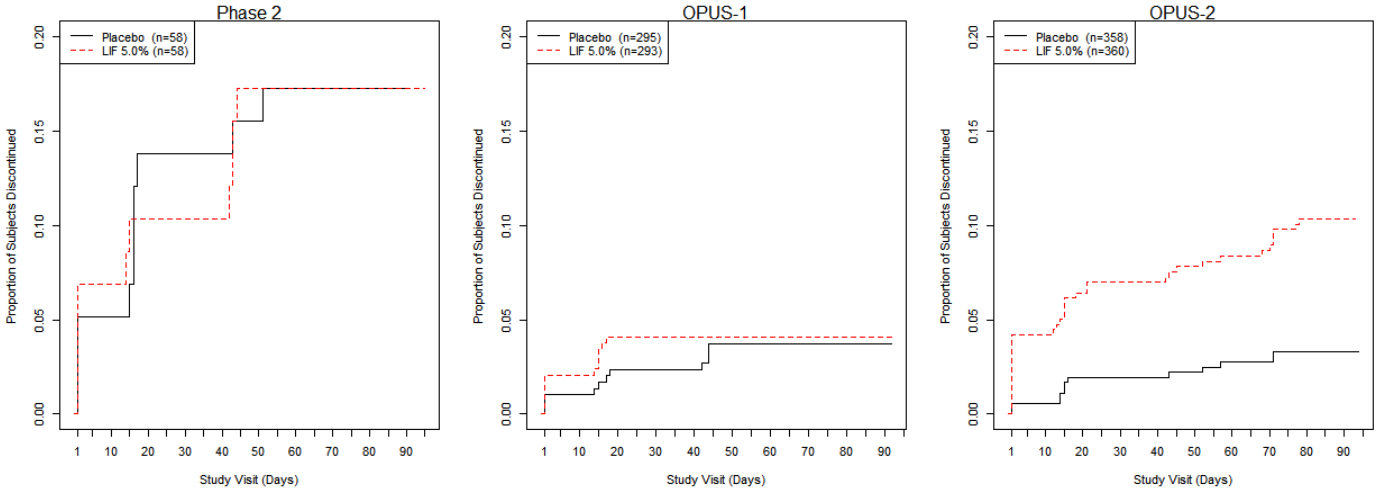
Of the 718 randomized subjects in OPUS- 2 study; a total of 49 (7%) subjects discontinued from the study before week 12; the discontinuation rate in the LIF 5.0% treated group was three times higher than in the placebo treated group (10% versus 3% in Placebo). Adverse event was the most common reason for discontinuation in the LIF 5.0% treated group (7% versus 1.0% in Placebo). In the LIF 5.0% treated group, approximately half of the discontinued subjects due to AE did so because of *blurred vision and burning upon investigational product instillation*.

The proportions of subjects discontinued in each study over time during the 12-week treatment period are shown in Figure 5. In the Phase 2 and OPUS-1 study, the discontinuation rate over time was comparable between the treatment groups. In the OPUS-2 study, on the other hand, the discontinuation rate at all visits were much higher in the LIF 5.0% treated group compared with in the Placebo treated group, and about half of the discontinued subjects in this group did so early on (before Day 42) in the study.

Figure 5: Proportion of Subjects Discontinued from Study
(All Randomized Subjects)



3.2.3.2 Demography

The summary of demographic and baseline characteristics for subjects in the ITT population are presented in Table 2.

In each study, the majority of patients were Caucasian (≥85%), more than 70% were female, and the average age of patients was about 60 years with 30-40% of patients at least 65 years old. The majority of subjects in each study had blue or brown iris color (≥ 65%).

Approximately 50% of subjects in the Phase 2 study and 44% of subjects in the OPUS-1 study had a history of artificial tear use whereas all subjects in the OPUS-2 study had a history of artificial tear use since it was one of the study inclusion criteria.

In each study, no marked difference between the treatment groups was observed in terms of the demographic characteristics.

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Table 2: Demographic Summary by Study and Treatment Group
(ITT Population)

	Phase 2		OPUS-1		OPUS-2	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 358)**	**LIF 5.0% (N = 360)**
Age						
Mean (SD)	60.4 (12.93)	62.3 (12.22)	61.1 (11.77)	60.2 (12.21)	58.9 (14.26)	58.7 (13.93)
Median	60.5	62.0	62.0	59.0	60.5	59.4
Range	26.0, 89.0	31.0, 85.0	24.0, 85.0	20.0, 91.0	19.8, 88.7	19.2, 97.5
Age Group, n (%)						
< 65	40 (69.0)	35 (60.3)	178 (60.3)	194 (66.2)	225 (62.5)	236 (65.9)
>= 65	18 (31.0)	23 (39.7)	117 (39.7)	99 (33.8)	135 (37.5)	122 (34.1)
Sex, n (%)						
Female	45 (77.6)	47 (81.0)	217 (73.6)	229 (78.2)	265 (73.6)	285 (79.6)
Male	13 (22.4)	11 (19.0)	78 (26.4)	64 (21.8)	95 (26.4)	73 (20.4)
Ethnicity, n (%)						
Hispanic or Latino	0 (0.0)	0 (0.0)	7 (2.4)	6 (2.0)	64 (17.8)	79 (22.1)
Not Hispanic or Latino	58 (100)	58 (100)	288 (97.6)	287 (98.0)	296 (82.2)	279 (77.9)
Race, n (%)						
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	2 (0.6)	4 (1.1)
Asian	1 (1.7)	3 (5.2)	2 (0.7)	3 (1.0)	14 (3.9)	19 (5.3)
Black or African American	3 (5.2)	2 (3.4)	11 (3.7)	16 (5.5)	34 (9.4)	30 (8.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	2 (0.6)
White	54 (93.1)	53 (91.4)	276 (93.6)	270 (92.2)	305 (84.7)	303 (84.6)
Other	0 (0.0)	0 (0.0)	4 (1.4)	3 (1.0)	2 (0.6)	0 (0.0)
Iris Color, n (%)						
Black	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)
Blue	20 (34.5)	21 (36.2)	98 (33.2)	105 (35.8)	86 (23.9)	80 (22.3)
Brown	21 (36.2)	18 (31.0)	96 (32.5)	113 (38.6)	189 (52.5)	193 (53.9)
Gray	1 (1.7)	1 (1.7)	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)
Green	6 (10.3)	3 (5.2)	27 (9.2)	18 (6.1)	35 (9.7)	27 (7.5)
Hazel	10 (17.2)	15 (25.9)	71 (24.1)	52 (17.7)	49 (13.6)	56 (15.6)
Other: Blue/Brown	--	--	0 (0.0)	1 (0.3)	--	--
Missing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	--	--
Artificial Tear Use, n (%) [1]						
No	29 (50.0)	27 (46.6)	165 (55.9)	165 (56.3)	0 (0.0)	0 (0.0)
Yes	29 (50.0)	31 (53.4)	130 (44.1)	128 (43.7)	360 (100)	358 (100)

Source: Table 4 of Phase 2, OPUS-1, and OPUS-2 Clinical Study Reports; [1] Based on reviewer analysis

3.2.3.3 Baseline Disease Characteristics

The descriptive summary for the key baseline sign and symptom variables are shown in Table 3; furthermore, the distributions for the sign variables are shown in Figure 6 and Figure 7 and for the symptom variables are shown in Figure 8. Overall, the baseline scores for the key sign and symptom variable were comparable between the treatment groups.

In the Phase 2 and OPUS-1 study, the mean baseline ICSS was about 1.8 and about 65% of subjects within each study had baseline ICSS >1.5; by design, the maximum baseline ICSS score in these studies was ≤ 3.0. In the OPUS-2 study, on the other hand, the mean baseline ICSS was slightly higher than in the Phase 2 and in OPUS-1 studies; in this study, the mean baseline ICSS was about 2.4 and about 85% of subjects in this study had baseline ICSS >1.5. Similar patterns were observed at baseline when sign was assessed using Total CSS, Nasal CLGSS, and STT.

For the key symptom variables, the mean baseline EDS in 0-100 scale (0 = no discomfort; 100=maximal discomfort) was about 52 in the Phase 2 study, about 40 in OPUS-1, and about 69 in OPUS-2; and about 38% of subjects in the Phase 2 study, 25% of subjects in OPUS-1, and

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67% of subjects in OPUS-2 had EDS ≥ 60 at baseline. Note that OPUS-2 study enrolled more symptomatic subjects by design (i.e., EDS ≥40 at baseline was required for eligibility). Similar patterns were observed at baseline when symptom was assessed using ODS, VR_OSDI, and Total OSDI scores.

Table 3: Baseline Disease Characteristics by Study and Treatment Group
(ITT Population)

	Phase 2		OPUS-1		OPUS-2	
Parameters	**Placebo (N = 58)**	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 360)**	**LIF 5.0% (N = 358)**
Key Sign Parameters						
ICSS:						
Mean	1.6 (0.51)	1.8 (0.51)	1.8 (0.60)	1.8 (0.60)	2.4 (0.72)	2.4 (0.76)
Median	2.0	2.0	2.0	2.0	2.5	2.5
Range	0.5, 2.5	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 4.0	0.5, 4.0
ICSS Category, n (%)						
≤ 1.5	22 (37.9)	19 (32.8)	105 (35.7)	95 (32.4)	47 (13.1)	46 (12.8)
> 1.5	36 (62.1)	39 (67.2)	189 (64.3)	198 (67.6)	313 (86.9)	312 (87.2)
Total CSS						
Mean	4.4 (1.20)	4.3 (1.06)	4.8 (1.38)	4.8 (1.40)	5.2 (2.01)	5.1 (2.08)
Median	4.3	4.0	4.5	4.5	4.5	4.5
Range	1.0, 7.0	2.5, 7.5	2.0, 9.5	2.0, 10.0	1.0, 11.5	1.0, 12.0
Nasal CLGSS:						
Mean	1.80 (0.93)	1.69 (0.77)	1.90 (0.84)	2.03 (0.81)	2.14 (1.05)	2.13 (1.04)
Median	2.00	2.00	2.00	2.00	2.50	2.00
Range	0.0, 4.0	0.0, 3.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0
STT (Un-anesthetized):						
Mean	4.7 (2.84)	5.0 (2.98)	4.7 (2.86)	4.9 (3.01)	5.1 (2.77)	5.5 (2.83)
Median	4.0	5.0	4.0	4.0	5.0	5.0
Range	1.0, 10.0	1.0, 10.0	1.0, 10.0	1.0, 10.0	0.0, 10.0	1.0, 10.0
Key Symptom Parameters						
EDS:						
Mean	51.8 (23.55)	51.6 (24.69)	41.6 (29.69)	40.2 (28.64)	69.2 (16.76)	69.7 (16.95)
Median	55.0	51.0	39.0	42.0	69.0	69.0
Range	0.0, 98.0	3.0, 100.0	0.0, 100.0	0.0, 100.0	40.0, 100.0	40.0, 100.0
EDS Category, n (%)						
< 40 [1]	17 (29.3)	19 (32.8)	148 (50.2)	137 (46.8)	NA	NA
40 – 50	7 (12.1)	7 (12.1)	20 (6.8)	28 (9.6)	52 (14.4)	43 (12.0)
50 – 60	11 (19.0)	10 (17.2)	45 (15.3)	55 (18.8)	67 (18.6)	76 (21.2)
≥ 60	23 (39.7)	22 (37.9)	82 (27.8)	73 (24.9)	241 (66.9)	239 (66.8)
VR_OSDI:						
Mean	1.0 (0.87)	1.2 (1.15)	0.9 (0.96)	0.9 (0.93)	1.4 (1.06)	1.5 (1.06)
Median	1.0	0.8	0.7	0.5	1.3	1.4
Range	0.0, 2.5	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0
Total OSDI:						
Mean	28.8 (16.50)	31.8 (21.31)	27.1 (18.15)	26.0 (19.04)	39.8 (20.43)	40.8 (21.84)
Median	29.6	27.3	22.7	20.8	39.6	37.5
Range	2.3, 60.4	2.8, 79.5	0.0, 75.0	0.0, 83.3	0.0, 93.8	0.0, 100.0
EDisS [2]:						
Mean	--	--	--	--	55.5 (24.93)	56.1 (25.39)
Median	--	--	--	--	56.5	56
Range	--	--	--	--	0.0, 100.0	0.0, 100.0
ODS:						
Mean	2.0 (1.17)	2.0 (1.04)	1.8 (1.16)	1.7 (1.19)	2.3 (1.08)	2.3 (1.03)
Median	2.0	2.0	2.0	2.0	3.0	2.0
Range	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0

[1] EDS ≥ 40 at Days -14 and 0 was required in the OPUS-2 study; [2] Not collected in the Phase 2 and OPUS-1 studies
ICSS: Inferior corneal staining score; Total CSS: Total corneal staining score; Nasal CLGSS: Nasal conjunctival lissamine green staining score; STT: Schirmer Tear Test (mm/5 minutes); EDS: Eye Dryness Score (VAS); OSDI: Ocular Surface Disease Index; VR_OSDI: Vision related OSDI; EDisS: Eye Discomfort Score (VAS); ODS: Ocular Discomfort Score.

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Figure 6: Distribution of Baseline ICSS (ITT Population)

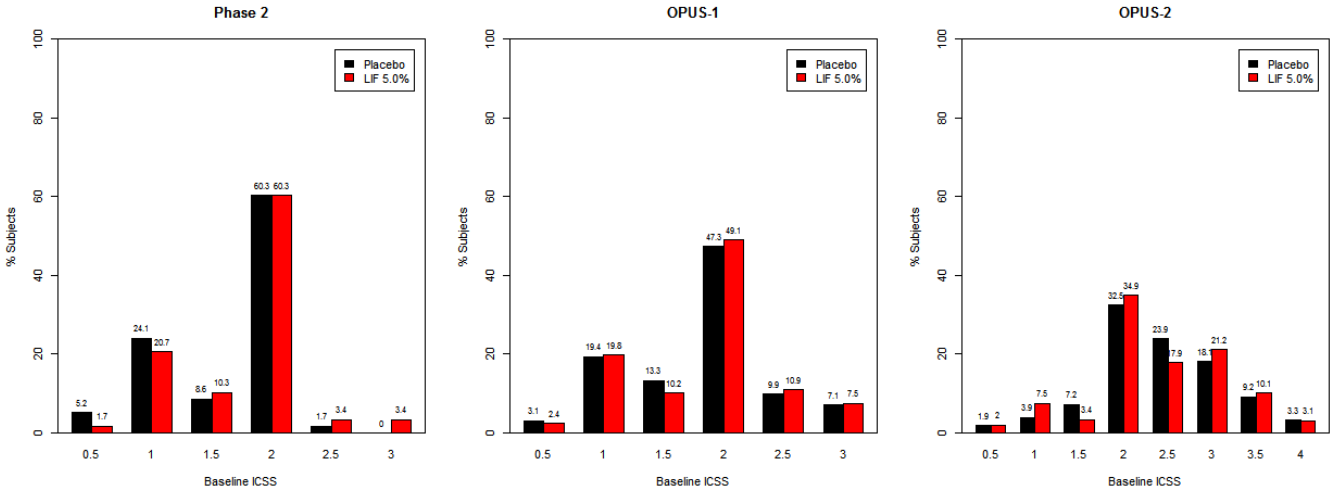


Figure 7: Distribution of Baseline Total CSS, Nasal CLGSS, and STT (ITT Population)

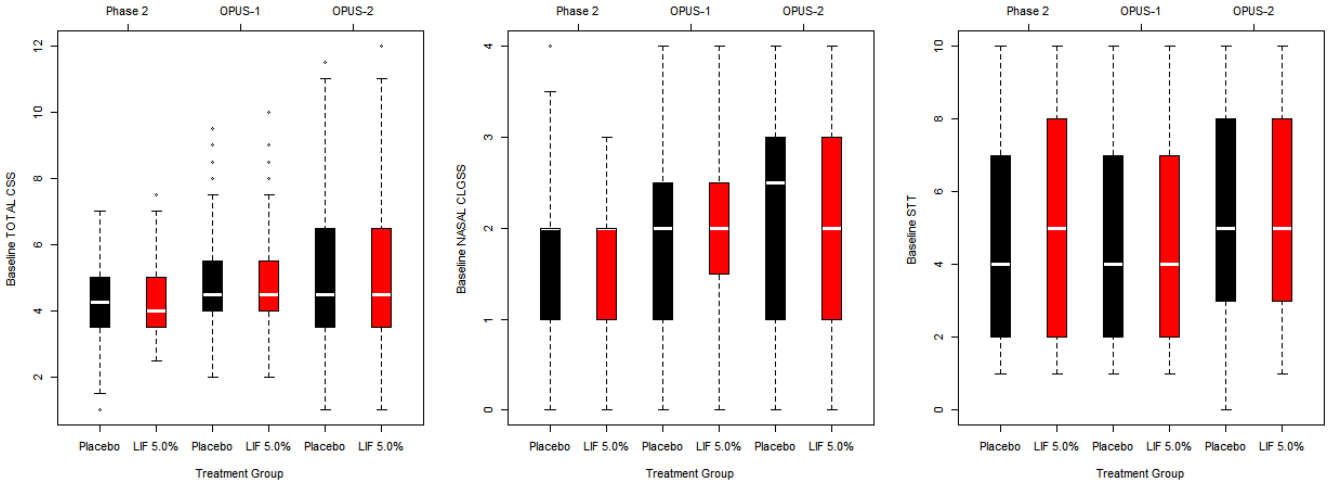
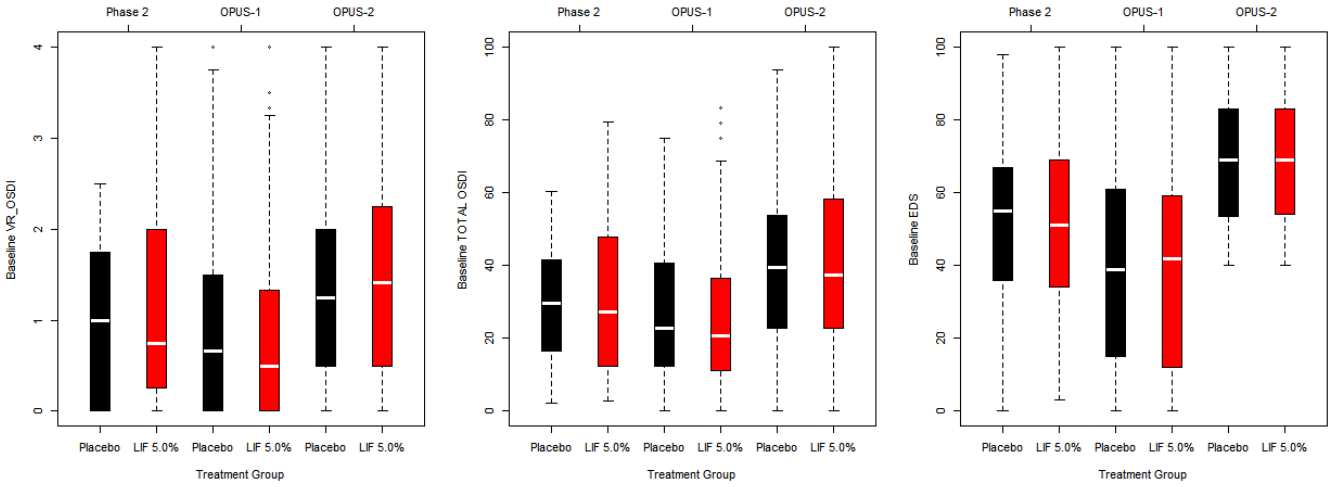


Figure 8: Distribution of Baseline VR_OSDI, Total OSDI, and EDS (ITT Population)



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3.2.4 Efficacy Results and Conclusions

The primary sign efficacy endpoint in each study was based on the inferior corneal staining score. The change from baseline in ICSS at Day 84 was the primary sign efficacy endpoint in OPUS-1 and OPUS-2 study while the actual ICSS at Day 84 was the primary sign efficacy endpoint in the Phase 2 study.

The change from baseline in VR_OSDI at Day 84 and the change from baseline in EDS at Day 84 were the co-primary symptom efficacy endpoints in OPUS-1 and OPUS-2 studies, respectively. There was no primary symptom efficacy endpoint defined in the Phase 2 study.

To compare LIF 5.0% ophthalmic solution againest Placebo in the sign and symptom endpoints, ANCOVA model was used in each study on the ITT population with LOCF for missing data. In the model, the change from baseline value at Day 84 was used as the response variable, and treatment, the baseline value, and the study specific strata (for OPUS-1 and OPUS-2) were used as covariates. Based on the model, the difference in the mean change between the treatment groups (LIF 5.0% minus Placebo) was determined using the least square means (LSM). The default observed margin (OM) option in the LSMEANS statement in SAS PROC MIXED was used to account for any imbalance in sample size and in the mean change values across strata.

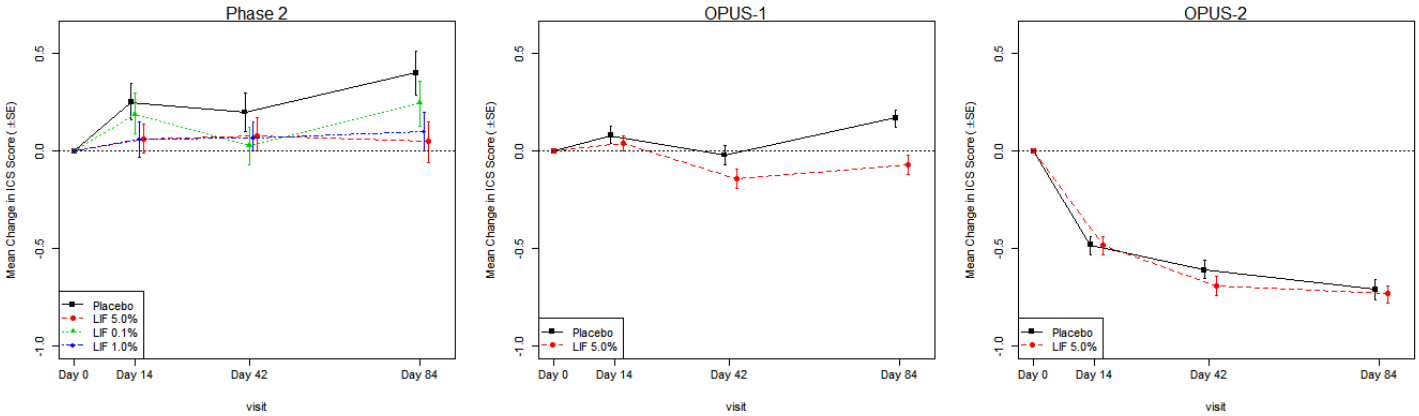
An unadjusted analysis based on a two sample t-test and a non-parametric Wilcoxon rank sum test was also performed in the three studies.

3.2.4.1 Co-Primary Endpoints

3.2.4.1.1 Primary Objective Endpoint: Inferior Corneal Staining Score (ICSS)

For each study, the mean changes in ICSS from baseline and standard errors (SE) at each visit were shown in Figure 9 below by treatment group.

Figure 9: Mean Change (±SE) in ICSS from Baseline at each Visit
(ITT Population, LOCF)



Source: Appendix Table 12; For the plot of the actual Mean in ICSS over time for each study, see Appendix Figure 32.

For the Phase 2 study, no reduction in ICSS was observed on average in the lifitegrast dose groups (LIF 0.1%, 1.0%, and 5.0%) as well as in the Placebo group throughout the study. However, a dose response in the mean change in ICSS was seen at Day 84. Since the greatest treatment effect was observed with LIF 5.0% dose group, the applicant studied this dose regimen

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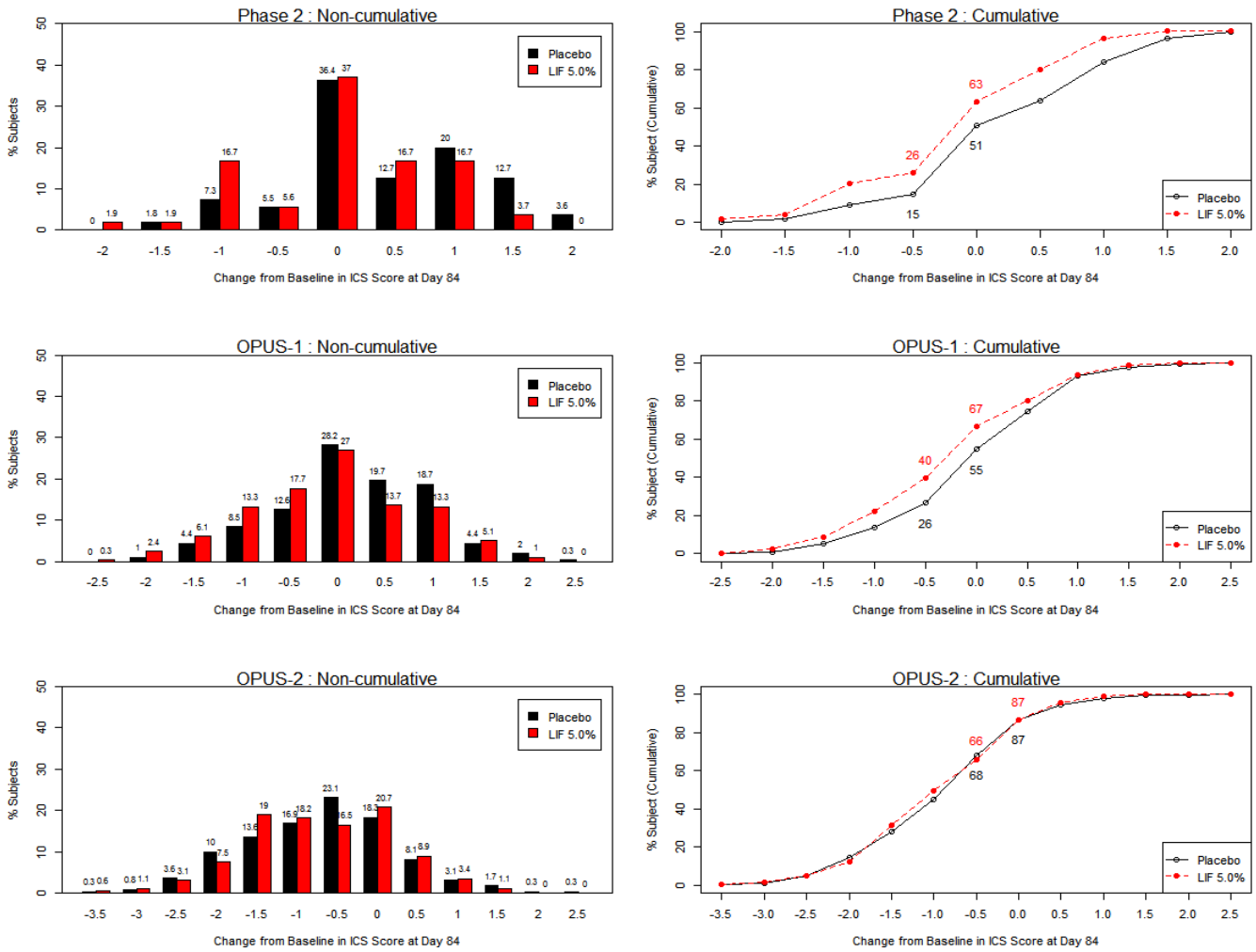
in the two Phase 3 studies. Therefore, for the phase 2 study in this review, only LIF 5.0% dose group was compared against Placebo with no multiplicity correction.

The mean changes in ICSS (±SE) from baseline at each visit for OPUS-1 and OPUS-2 studies were also shown in Figure 9. In OPUS-1 study, a clear separation in the mean change in ICSS was seen between the treatment groups as early as at Day 42, and it was maintained at the end of treatment period at Day 84 even though the magnitude of reduction observed at Day 42 was not maintained at Day 84 in both treatment groups.

In OPUS-2 study, both LIF 5.0% and Placebo group demonstrated larger mean reduction in ICSS compared with in the Phase 2 and OPUS-1 studies; in this study, the mean reductions between the treatment groups was comparable. Note that the Placebo group in OPUS-2 study, unlike in the Phase 2 and OPUS-1, demonstrated large mean reductions in ICSS throughout the treatment period. This was most likely due to the higher mean baseline score in OPUS-2 study than in the other studies (See Table 3); thus, in a more sever population with high baseline sign and symptom score, the Placebo solution which has a lubricant effect showed a considerable effect in improving clinical sign.

Figure 10: Distribution of change in ICSS from Baseline at Day 84
(ITT Population, LOCF)



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The distributions (both cumulative and non-cumulative) of the change in ICSS from baseline at Day 84 are shown in Figure 10 for all three studies.

In the Phase 2 and OPUS-1 studies, respectively, about 26% and 40% of LIF 5.0% treated subjects showed some form of reduction in ICSS compared with 15% and 26% of Placebo treated subjects. In the OPUS-2 study, a lot more subjects, about 66% of LIF 5.0% treated subjects and 68% of Placebo treated subjects, showed at least some form of reduction in ICSS at Day 84. In each treatment group, approximately 36% of subjects in the Phase 2 study, 27% of subjects in the OPUS-1 study, and 19% of subjects in the OPUS-2 study had no change in ICSS from baseline at Day 84. On the other hand, some form of worsening in ICSS from baseline at Day 84 was observed by 37%, 33%, and 13% of LIF 5.0% treated subjects compared with 49%, 45%, and 13% of placebo treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively.

In each study, the mean change in ICSS from baseline at Day 84 was compared between LIF 5.0% and Placebo treated groups using ANCOVA model. The summary of ICSS at baseline, Day 84, and the change from baseline at Day 84 based on the ITT population using the LOCF method are shown in Table 4.

Table 4: Mean Change in ICSS from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Summary	Placebo (N=58)	LIF 5.0% (N=58)	Placebo (N=294)	LIF 5.0% (N=293)	Placebo (N=360)	LIF 5.0% (N=358)
Baseline						
N	58	58	294	293	360	358
Mean (SD)	1.65 (0.513)	1.77 (0.515)	1.81 (0.599)	1.84 (0.597)	2.40 (0.722)	2.39 (0.763)
Median	2.00	2.00	2.00	2.00	2.50	2.50
(95% CI)	(1.51, 1.78)	(1.63, 1.90)	(1.75, 1.88)	(1.78, 1.91)	(2.33, 2.47)	(2.31, 2.47)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	2.05 (0.715)	1.83 (0.680)	1.98 (0.874)	1.77 (0.879)	1.69 (1.010)	1.66 (1.044)
Median	2.00	2.00	0.00	2.00	1.50	1.50
(95% CI)	(1.85, 2.24)	(1.65, 2.02)	(1.88, 2.08))	(1.67, 1.87)	(1.59, 1.80)	(1.55, 1.77)
Change from Baseline to Day 84						
Mean (SD)	0.40 (0.802)	0.05 (0.773)	0.17 (0.819)	-0.07 (0.868)	-0.71 (0.943)	-0.73 (0.926)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
95% CI	(0.18, 0.62)	(-0.16, 0.26)	(0.07, 0.26)	(-0.17, -0.04)	(-0.80, -0.61)	(-0.83, -0.64)
Based on adjusted analysis [1]:						
LS Means (SE)	0.35 (0.093)	0.10 (0.094)	0.16 (0.05)	-0.07 (0.05)	-0.7 (0.047)	-0.7 (0.05)
Diff.(minus Placebo) (95% CI)		-0.25 (-0.51, 0.02)		-0.23 (-0.36, -0.09)		-0.03 (-0.16, 0.10)
P-value: ANCOVA		0.0666		0.0007		0.6122
Based on unadjusted analysis:						
P-value: Student T-test		0.0209		0.0007		0.6562
P-value: Wilcoxon Test		0.0384		0.0006		0.7849

[1] Based on ANCOVA model that adjusted for the baseline ICS score in the phase 2 study and for the baseline and stratification factors in the OPUS-1 and OPUS-2 studies.

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In OPUS-1 study, LIF 5.0% treated group showed numerically larger mean reduction in ICSS from baseline at Day 84 compared with Placebo. The mean change in ICSS at Day 84 in the LIF 5.0% treated group was -0.07 (95% CI: -0.17, -0.04) and in the Placebo treated group was +0.17 (95% CI: 0.07, 0.26); the treatment difference (*LIF 5.0% minus Placebo*) was -0.23 (95% CI: -0.36, -0.09) and statistical significant difference was achieved in this study (p-value = 0.0007).

In the Phase 2 study, both LIF 5.0% and Placebo treated groups did not show mean reduction in ICSS from baseline throughout the study; however, a dose response in the mean change in ICSS was seen at Day 84 (See Figure 9). The mean change in ICSS at Day 84 in the LIF 5.0% treated group was +0.05 (95% CI: -0.16, 0.26) and in the Placebo treated group was +0.40 (95% CI: 0.18, 0.62); the treatment difference was -0.25 (95% CI: -0.51, 0.02) and not statistically significant (p-value = 0.0666). Though not statistically significant, the magnitude of treatment difference seen in this study (-0.25) was very close to what was seen in OPUS-1 study (-0.23); the non-statistical significant result in the Phase 2 study was likely due to smaller sample size compared with OPUS-1 study (note that the p-value in the Phase 2 study was close to 0.05).

In the OPUS-2 study, both treatment groups showed numerically larger mean reductions in ICSS throughout the study compared with in the Phase 2 and OPUS-1 studies. In this study, both treatment group demonstrated comparable mean reductions in ICSS at Day 84: the mean change in ICSS at Day 84 in the LIF 5.0% treated group was -0.73 (95% CI: -0.83, -0.64) and in the Placebo treated group was -0.71 (95% CI: -0.80, -0.61); the treatment difference was -0.03 (95% CI: -0.16, 0.10) and not statistically significant (p-value = 0.6122).

It should be noted that the larger mean reduction in ICSS observed in OPUS-2 study compared with in the Phase 2 and OPUS-1 studies was mainly due to the higher mean baseline score seen in OPUS-2 study than in the Phase 2 and OPUS-1 studies, and the lack of treatment difference in OPUS-2 study (in subjects with moderate-to-sever symptom) may be attributed to insufficient study duration. Note that the mean baseline ICSS in the Phase 2 and OPUS-1 studies and the mean ICSS at Day 84 in the OPUS-2 study (after treatment was received for 84 days) were comparable (See Table 4). Therefore, in order to see any separation between the treatment groups in OPUS-2 study that was seen in the Phase 2 and OPUS-1 studies, longer study duration may be needed.

In summary, statistical superiority in improving the clinical sign (as measured using ICSS) was demonstrated in only OPUS-1 study. In the Phase 2 and OPUS-2 studies, on the other hand, LIF 5.0% did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

The mean changes in ICSS from baseline at Days 14 and 42 were also compared between LIF 5.0% and Placebo group. The results are presented in Appendix Table 12.

3.2.4.1.2 Primary Subjective Endpoint in OPUS-1 Study: VR_OSDI Subscale Score

The change in VR_OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study and was supportive symptom endpoint in the Phase 2 and OPUS-2 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-2 studies were intended for descriptive use.

The efficacy results for the mean change in VR_OSDI score from baseline at each visit are shown in Figure 11 for each study.

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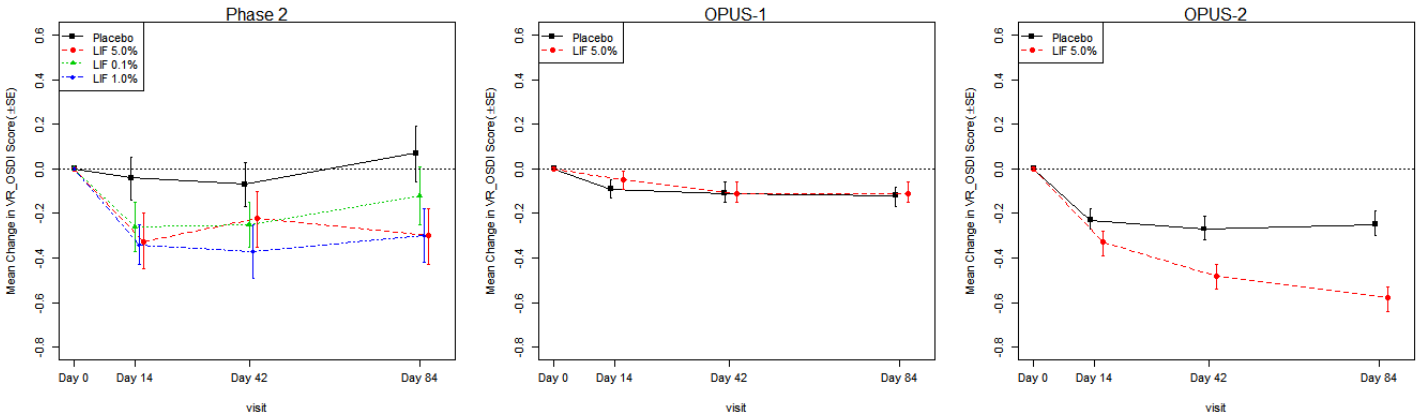
In the Phase 2 study, LIF 5.0% treated group demonstrated a relatively larger mean reductions in VR_OSDI score throughout the study compared with Placebo treated group; clear separations in the mean reductions in VR_OSDI score was seen between the treatment groups early on at Day 14 and then at the end of the study on Day 84. In the OPUS-1 study, both treatment groups demonstrated marginal reductions in VR_OSDI score from baseline throughout the study, and the rate of reductions was virtually the same between the treatment groups.

In the OPUS-2 study, both treatment groups demonstrated numerically larger mean reduction in VR_OSDI score from baseline throughout the study compared with in the Phase 2 and OPUS_1 studies; in this study, the mean reductions in the LIF 5.0% treated group was larger than in the Placebo treated group throughout the study.

Figure 11: Mean Change (± SE) in VR_OSDI from Baseline at each Visit



Source: Appendix Table 13. For the plot of the actual mean in VR_OSDI score over time for each study, see Appendix Figure 32.

The distributions of the change in VR_OSDI score from baseline at Day 84 (using kernel density estimations and cumulative distributions) are shown in Figure 12 for all three studies. In the OPUS-1 study, the distributions for the two treatment groups were virtually the same. In the Phase 2 and OPUS-2 studies, on the other hand, the distributions of the change in VR_OSDI score at Day 84 for LIF 5.0% treated subjects was shifted slightly towards the left compared with the distributions for Placebo treated subjects; that is, in these studies more LIF 5.0% treated subjects demonstrated some form of reductions and fewer LIF 5.0% treated subjects demonstrated some form of worsening compared with Placebo treated subjects.

Table 5: Proportion of Subjects with Mean Change in VR_OSDI at Day 84
(ITT Populaion, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Change	Placebo	LIF 5.0%	Placebo	LIF 5.0%	Placebo	LIF 5.0%
Change < 0	14 (25.4)	26 (48.2)	113 (38.3)	114 (39.0)	179 (49.9)	224 (62.8)
No Change (= 0)	16 (29.1)	12 (22.2)	85 (28.8)	89 (30.5)	66 (18.4)	59 (16.5)
Change > 0	25 (45.4)	16 (29.6)	97 (32.9)	89 (30.5)	114 (31.7)	74 (20.7)

The proportions of subjects with some form of reductions, with no change, or with some form of worsening in VR_OSDI score from baseline at Day 84 are shown in Table 5 and Figure 12 (cumulative distribution) for each study. For example, 23%, 1%, and 13% more LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed some form of reductions compared with Placebo treated subjects. On the other hand, 16%, 2%, and 11% fewer LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed

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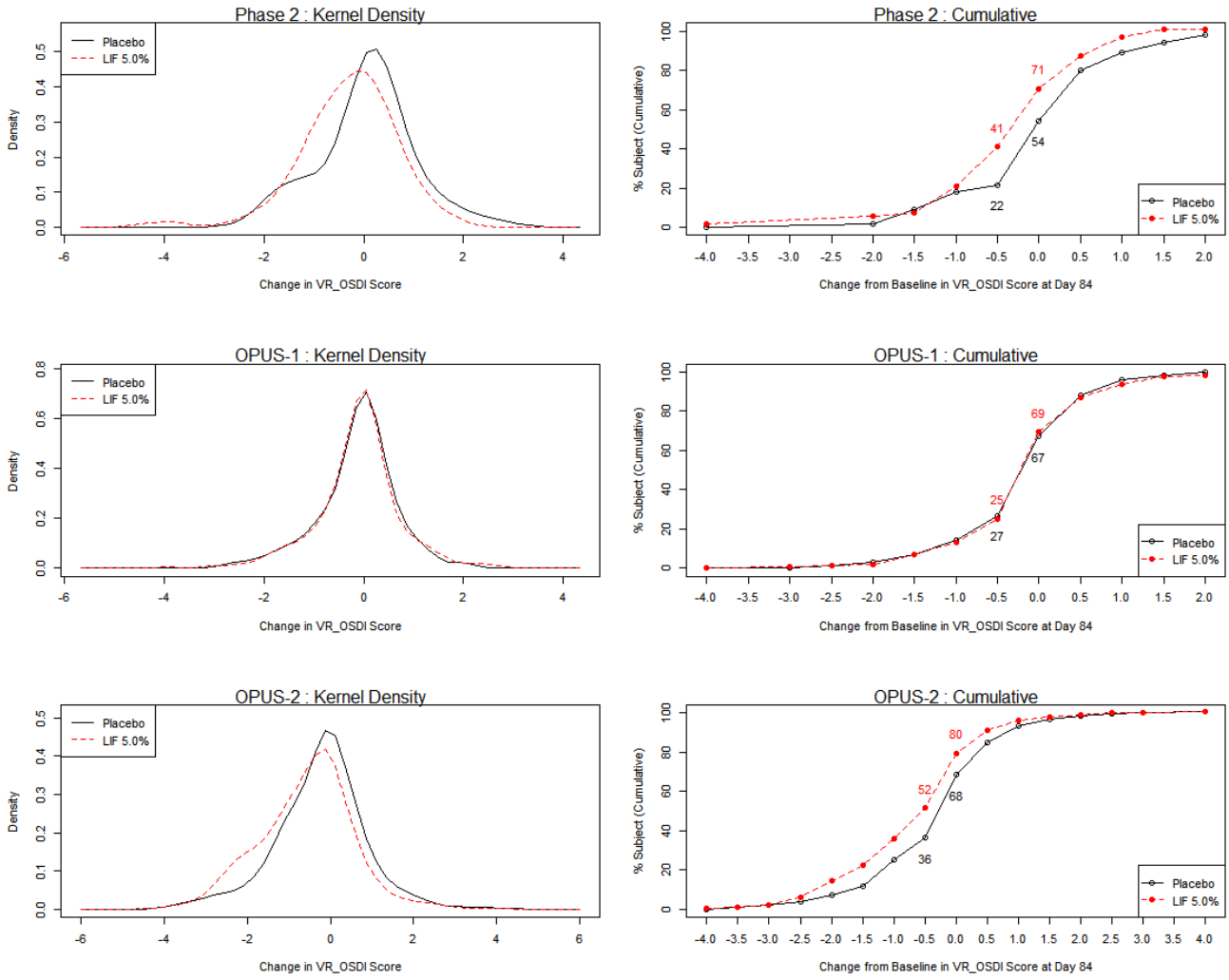
some form of worsening compared with Placebo treated subjects. Additionally, about the same percentage of subjects in each treatment group in OPUS-1 and OPUS-2 studies, and a slightly higher percentage of Placebo treated subjects in the Phase 2 study showed no change in VR_OSDI score from baseline at Day 84 (29% in Placebo versus 22% in LIF 5.0%).

Figure 12: Distribution of Change in VR_OSDI from Baseline at Day 84
(ITT Population, LOCF)



In each study, the mean change in VR_OSDI score from baseline at Day 84 was compared between LIF 5.0% and Placebo treated group using ANCOVA model. The summary of the VR_OSDI score at baseline, Day 84, and the change from baseline at Day 84 based on the ITT population using the LOCF method are shown in Table 6.

In the Phase 2 study, LIF 5.0% treated group showed numerically slightly larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group. The mean change in VR_OSDI score from baseline at Day 84 in the LIF 5.0% treated group was -0.30 (95% CI: -0.56, -0.05) and in the Placebo treated group was +0.07 (95% CI: -0.18, 0.32); the treatment difference was -0.30 (95% CI: -0.63, 0.03; p-value = 0.0712).

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In the OPUS-1 study, both treatment groups showed small and comparable mean reductions in VR_OSDI score from baseline throughout the study. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.11 (95% CI: -0.20, -0.01) and in the Placebo treated group was -0.12 (95% CI: -0.21, -0.04); the treatment difference was -0.01 (95% CI: -0.12, 0.10) and not statistically significant (p-value = 0.8261).

In OPUS-2 study, both treatment groups demonstrated larger mean reductions in VR_OSDI score from baseline throughout the study compared to in the Phase 2 and OPUS-1 studies. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.58 (95% CI: -0.70, -0.47) and in the Placebo treated group was -0.25 (95% CI: -0.36, -0.14); the treatment difference was -0.28 (95% CI: -0.41, -0.14; p-value < 0.0001).

Table 6: Mean Change in VR_OSDI from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	295	293	360	358
Mean (SD)	0.96 (0.865)	1.16 (1.148)	0.93 (0.958)	0.86 (0.931)	1.38 (1.065)	1.48 (1.062)
Median	1.00	0.75	0.67	0.50	1.25	1.42
(95% CI)	(0.74, 1.19)	(0.86, 1.46)	(0.82, 1.04)	(0.75, 0.96)	(1.27, 1.49)	(1.37, 1.59)
Day 84						
N	55	54	295	292	359	357
Mean (SD)	1.05 (1.173)	0.88 (0.961)	0.80 (0.838)	0.75 (0.861)	1.13 (1.047)	0.90 (0.998)
Median	0.67	0.67	0.50	0.50	1.00	0.50
(95% CI)	(0.74, 1.37)	(0.62, 1.14)	(0.71, 0.90)	(0.65, 0.85)	(1.03, 1.24)	(0.80, 1.01)
Change from Baseline to Day 84						
Mean (SD)	0.07 (0.929)	-0.30 (0.934)	-0.12 (0.762)	-0.11 (0.829)	-0.25 (1.069)	-0.58 (1.100)
Median	0.00	0.00	0.00	0.00	0.00	-0.50
(95% CI)	(-0.18, 0.32)	(-0.56, -0.05)	(-0.21, -0.04)	(-0.20, -0.01)	(-0.36, -0.14)	(-0.70, -0.47)
Based on adjusted analysis [1]:						
LS Means (SE)	0.03 (0.116)	-0.27 (0.117)	-0.11 (0.039)	-0.12 (0.039)	-0.28 (0.048)	-0.55 (0.048)
Diff.(minus Placebo) (95% CI)		-0.30 (-0.63, 0.03)		-0.01 (-0.12, 0.10)		-0.28 (-0.41, -0.14)
P-value: ANCOVA		0.0712		0.8261		<0.0001
Based on unadjusted analysis:						
P-value: Student T-test		0.0394		0.7860		<0.0001
P-value: Wilcoxon Test		0.0393		0.9063		<0.0001

[1] Based on ANCOVA model that adjusted for baseline VR_OSDI score in the phase 2 study and for the baseline VR_OSDI score and stratification factors in the OPUS-1 and OPUS-2 studies.

In summary, statistical superiority in improving the pre-defined clinical symptom endpoint (using VR_OSDI score) at Day 84 was not demonstrated in OPUS-1 study. In OPUS-2 study, LIF 5.0% treated subjects demonstrated a much larger improvement in VR_OSDI over Placebo and in the Phase 2 study showed a moderate improvement over Placebo. Additionally, a dose response improvement in VR_OSDI was seen at Day 84 (see Figure 11) in the Phase 2 study.

The mean changes in VR_OSDI score from baseline at Days 14 and 42 were also compared between LIF 5.0% and Placebo treated groups. The results are presented in Appendix Table 13.

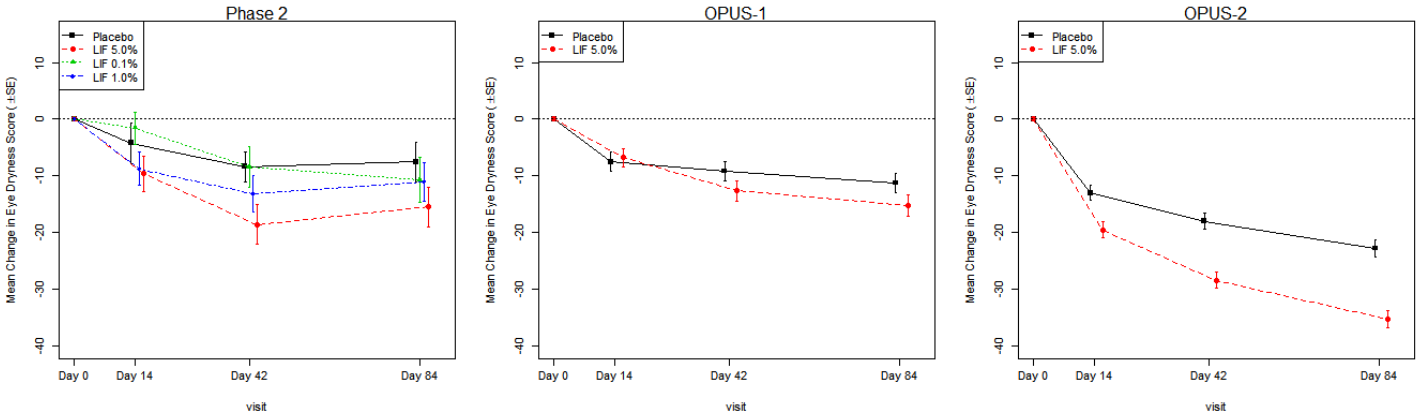
Reference ID: 3938302

3.2.4.1.3 Primary Subjective Endpoint in OPUS-2 Study: Eye Dryness Score (EDS)

The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2 and was supportive symptom endpoint in the Phase 2 and OPUS-1 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-1 studies were intended for descriptive use.

The efficacy results for the mean change in EDS from baseline at each visit are shown in Figure 13 for each study. Within each study, both treatment groups demonstrated large mean reductions in EDS at each visit; however, the mean reductions in the LIF 5.0% treated group were numerically larger than in the Placebo treated group throughout the study. Clear separations between the treatment groups were seen early on at Day 14 in the Phase 2 and OPUS-2 studies and at Day 42 in the OPUS-1 study.

Figure 13: Mean Change (± SE) in EDS from Baseline at each Visit
(ITT Population, LOCF)



Source: Table 14; For the plot of the actual Mean in EDS over time for each study, see Appendix Figure 32.

The distributions of the change in EDS from baseline at Day 84 (using kernel density estimations and cumulative distributions) are shown in Figure 14 for all three studies.

The distributions of the change in EDS at Day 84 for LIF 5.0% treated group was slightly shifted to the left in the Phase 2 and OPUS-1 studies and more shifted to the left in the OPUS-2 study compared with placebo treated group; that is, more LIF 5.0% treated subjects demonstrated some form of reductions and fewer LIF 5.0% treated subjects demonstrated some form of worsening compared with Placebo treated subjects.

In Table 7 below, the proportions of subjects with some form of reduction, no change, or with some form of worsening are shown. For example, 10%, 5%, and 13% more LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed some form of reductions compared with Placebo treated subjects. On the other hand, 5%, 5%, and 12% fewer LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed some form of worsening compared with Placebo treated subjects. A small percentage of subjects in each treatment group of each study showed no change in EDS from baseline at Day 84.

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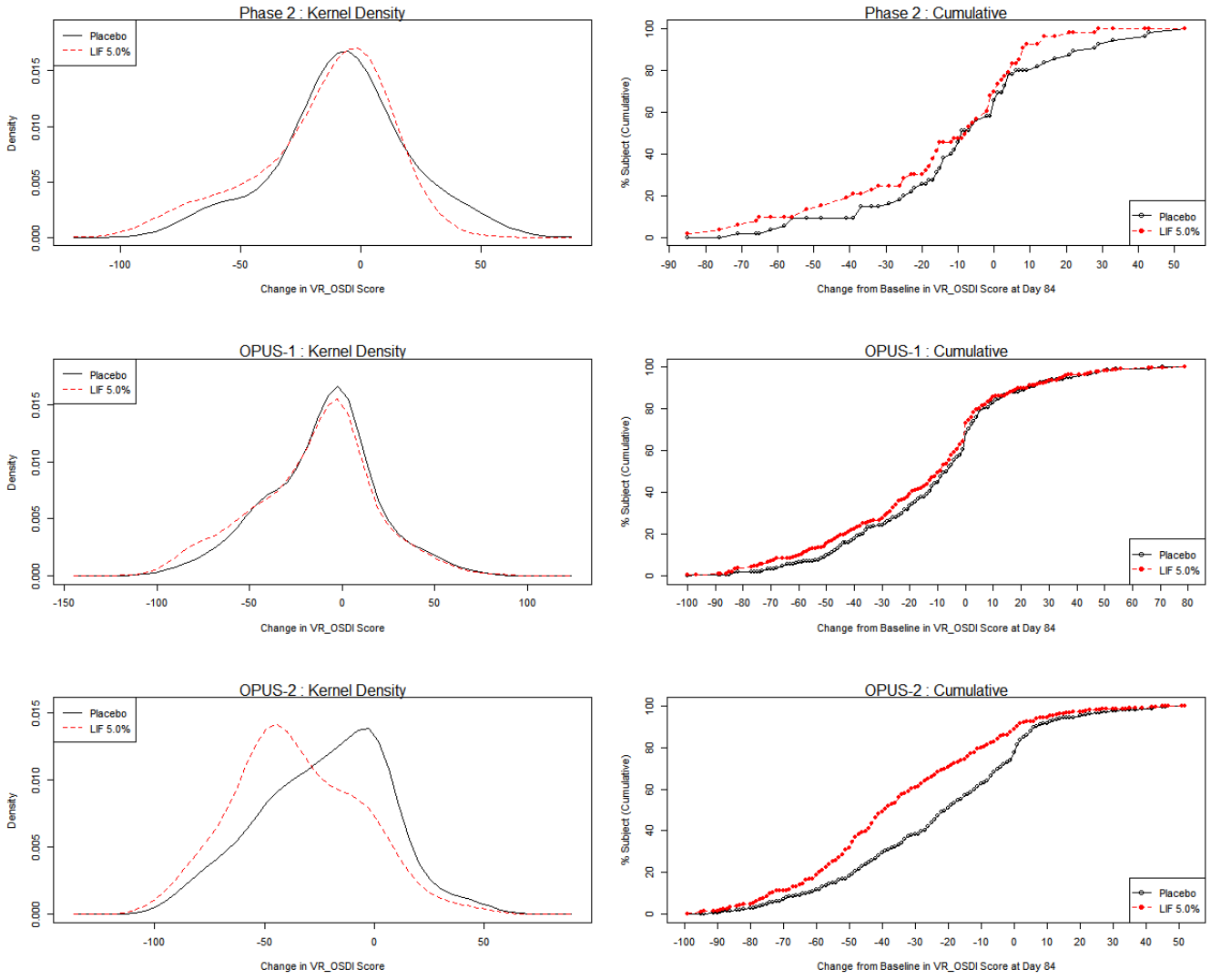
Table 7: Proportion of Subjects with Mean Change in EDS at Day 84
(ITT Population, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Change	Placebo	LIF 5.0%	Placebo	LIF 5.0%	Placebo	LIF 5.0%
Change < 0	32 (58.2)	36 (67.9)	178 (60.4)	189 (64.5)	265 (73.6)	312 (87.1)
No Change (= 0)	4 (7.3)	1 (1.9)	24 (8.1)	25 (8.5)	14 (4.0)	6 (1.7)
Change > 0	19 (34.5)	16 (30.2)	93 (31.5)	79 (27.0)	81 (22.5)	40 (11.2)

Figure 14: Distribution of Change in EDS from Baseline at Day 84
(ITT Population, LOCF)



In each study, the mean change in EDS from baseline at Day 84 between LIF 5.0% and Placebo treated group were compared using ANCOVA model. The summary of EDS data at baseline, Day 84, and the change from baseline at Day 84 based on the ITT population using the LOCF method are shown in Table 8. Both treatment groups within each study displayed some form of improvement in EDS from baseline at Day 84.

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Table 8: Summary of Mean Change in EDS from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	57	295	293	360	358
Mean (SD)	51.81 (23.552)	51.58 (24.688)	41.62 (29.690)	40.18 (28.645)	69.22 (16.761)	69.68 (16.954)
Median	55.00	51.00	39.00	42.00	69.00	69.00
(95% CI)	(45.62, 58.00)	(45.03, 58.13)	(38.22, 45.02)	(36.88, 43.47)	(67.48, 70.95)	(67.92, 71.44)
Day 84						
N	55	54	295	293	360	358
Mean (SD)	44.11 (27.130)	37.06 (27.578)	30.39 (30.773)	25.00 (28.870)	46.47 (29.875)	34.39 (27.862)
Median	47.00	35.00	19.00	11.00	50.00	28.00
(95% CI)	(36.77, 51.44)	(29.53, 44.58)	(26.86, 33.91)	(21.68, 28.32)	(43.37, 49.56)	(31.49, 37.28)
Change from Baseline to Day 84						
N	55	53	295	293	360	358
Mean (SD)	-7.55 (25.929)	-15.49 (25.987)	-11.23 (28.783)	-15.17 (31.482)	-22.75 (28.600)	-35.30 (28.400)
Median	-9.00	-7.00	-6.00	-9.00	-20.00	-39.00
(95% CI)	(-14.55, -0.54)	(-22.65, -8.33)	(-14.53, -7.94)	(-18.79, -11.55)	(-25.71, -19.79)	(-38.25, -32.34)
Based on adjusted analysis [1]:						
LS Means (SE)	-7.70 (3.240)	-15.3 (3.301)	-10.9 (1.530)	-15.5 (1.536)	-22.9 (1.450)	-35.2 (1.454)
Diff.(minus Placebo) (95% CI)		-7.63 (-16.8, 1.54)		-4.68 (-8.94, -0.43)		-12.3 (-16.4, -8.30)
P-value: ANCOVA		0.1021		0.0311		<0.0001
Based on un-adjusted analysis:						
P-value: Student T-test		0.1148		0.1137		<0.0001
P-value: Wilcoxon Test		0.2890		0.1376		<0.0001

[1] Based on ANCOVA model that adjusted for baseline EDS in the phase 2 study and for baseline EDS and stratification factors in the OPUS-1 and OPUS-2 studies.

LIF 5.0% treated subjects in the Phase 2 study showed numerically better improvement in EDS over Placebo. In this study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.5 (95% CI: -22.6, -8.3) and in the Placebo treated group was -7.6 (95% CI: -14.6, -0.5); the treatment difference was -7.6 (95% CI: -16.8, 1.5; p-value = 0.1021). Note that the confidence interval for the treatment difference did not exclude zero, and this was likely due to the smaller sample size.

LIF 5.0% treated subjects in the OPUS-1 study also showed numerically better improvement in EDS over Placebo. In this study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.2 (95% CI: -18.8, -11.6) and in the Placebo treated group was -11.2 (95% CI: -14.5, -7.9); the treatment difference was -4.7 (95% CI: -8.9, -0.4; p-value = 0.0311).

In this study, a much larger improvement in EDS from baseline at Day 84 was seen in a small subgroup of subjects with a recent history of ATU and with baseline EDS ≥40 (N = 67 in Placebo and N = 63 in LIF 5.0%). In this subgroup (see Figure 15 and Appendix Table 21), the mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.4 (95% CI: -43.4, -27.4) and in the Placebo treated group was -22.1 (95% CI: -29.8, -14.4); the treatment difference was -15.3 (95% CI: -25.9, -4.7).

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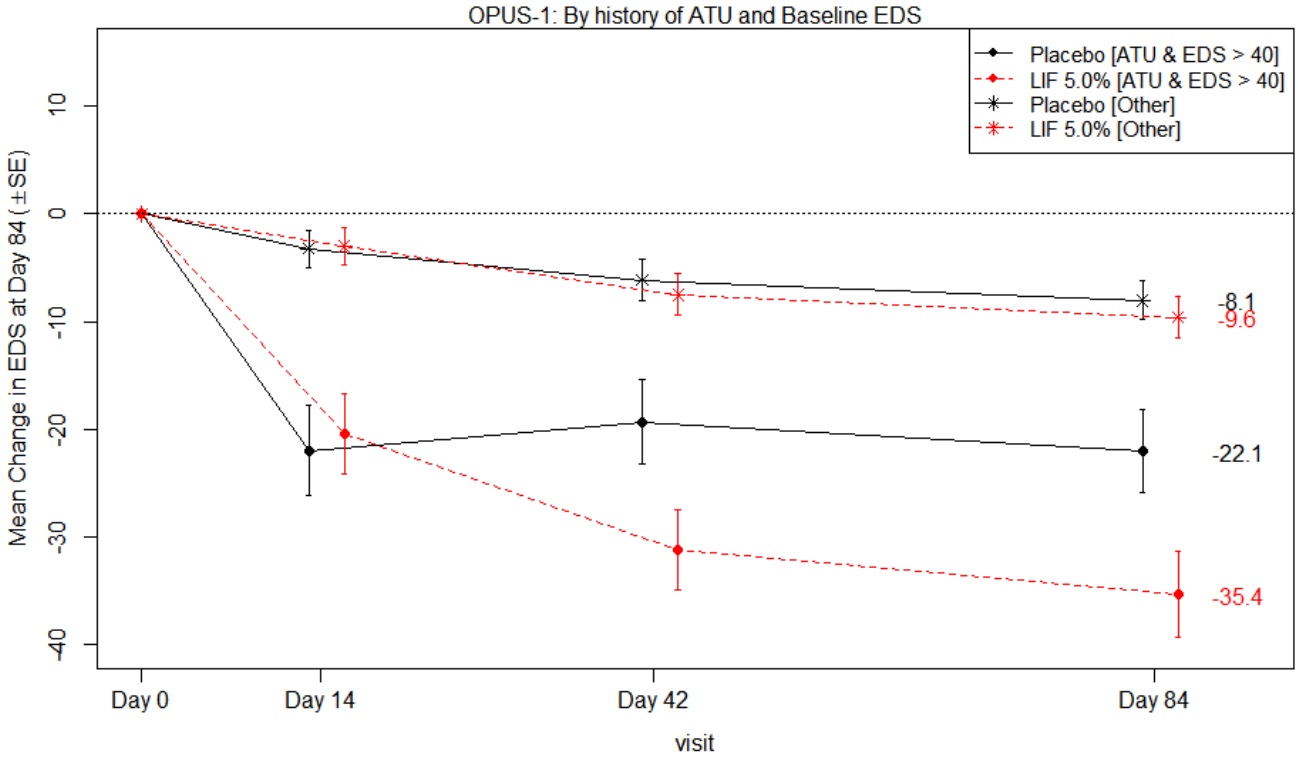
Note that the considerable improvement in EDS seen in the subgroup of subjects in the OPUS-1 study led to the design of OPUS-2 study, and as such, the OPUS-2 study enrolled subjects with a recent history of ATU and with baseline EDS ≥ 40, and used EDS as a co-primary symptom endpoint in the study.

Therefore, as was seen in the subgroup of patients in the OPUS-1 study, both treatment groups in the OPUS-2 study demonstrated large mean reduction in EDS throughout the study; and the mean reduction at Day 84 in the LIF 5.0% treated group was higher than in the Placebo treated group by about 12 units. In this study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.3 (95% CI: -38.3, -32.3) and in the Placebo treated group was -22.8 (95% CI: -25.7, -19.8); the treatment difference was -12.3 (95% CI: -16.4, -8.3) and was strongly statistically significant (p-value < 0.0001).

Figure 15: Mean Change (± SE) in EDS by History of ATU and Baseline EDS in OPUS-1 (ITT Population, LOCF)



Source: Appendix Table 21

In summary, both treatment groups within each study demonstrated large mean reductions in EDS from baseline throughout the study; statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated in OPUS-2 study. Both the Phase 2 and OPUS-1 studies showed numerically better improvement in EDS in the LIF 5.0% treated subjects over Placebo. Additionally, a dose response improvement in EDS was seen at Day 84 (see Figure 13) in the Phase 2 study.

In each study, the mean changes in EDS at Days 14 and 42 were also compared between the LIF 5.0% and Placebo treated groups. The results are presented in Appendix Table 14.

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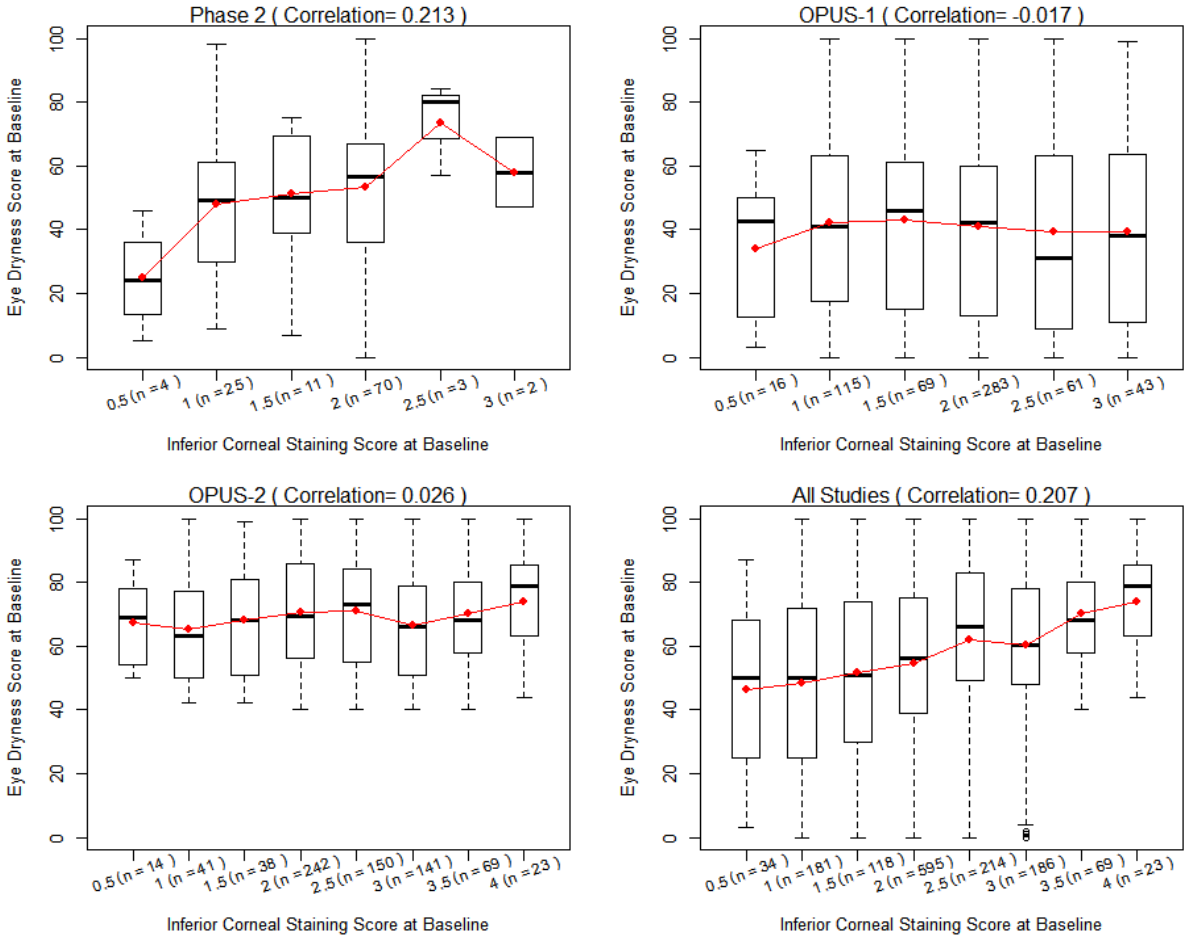
3.2.4.2 Relationship between the Co-primary Efficacy Endpoints

In this NDA application, superiority of LIF 5.0% over Placebo in improving clinical sign or clinical symptom of dry eye was not demonstrated in two or more studies; significant improvement in ICSS was demonstrated in OPUS-1 study while significant improvement in EDS and in VR_OSDI was demonstrated in OPUS-2 study. To study the association between the sign and symptom of dry eye, we examined the relationship between ICSS and EDS at baseline (before treatment was received) and at Day 84 (after treatment was received for 84 days) using data from the two Phase 3 and Phase 2 studies.

Baseline ICSS by Baseline EDS

The plots of baseline ICSS by baseline EDS based on data from each individual study and from the pooled study are shown in Figure 16. In the OPUS-1 and OPUS-2 studies, no apparent relationship was seen between ICSS and EDS at baseline; however; a slight increase in EDS with an increase in ICSS (correlation = 0.21) was seen based on the Phase 2 and the pooled data.

Figure 16: Relationship between ICSS and EDS at Baseline
(ITT Population)



ICSS AT Day 84 by EDS at Day 84

The plots of ICSS at Day 84 by EDS at Day 84 are shown in Figure 17 by treatment group for each study. A slight increase in EDS with an increase in ICSS was seen in LIF 5.0% treated group in the OPUS-1 study (correlation = 0.19) and in Placebo treated group in the OPUS-2

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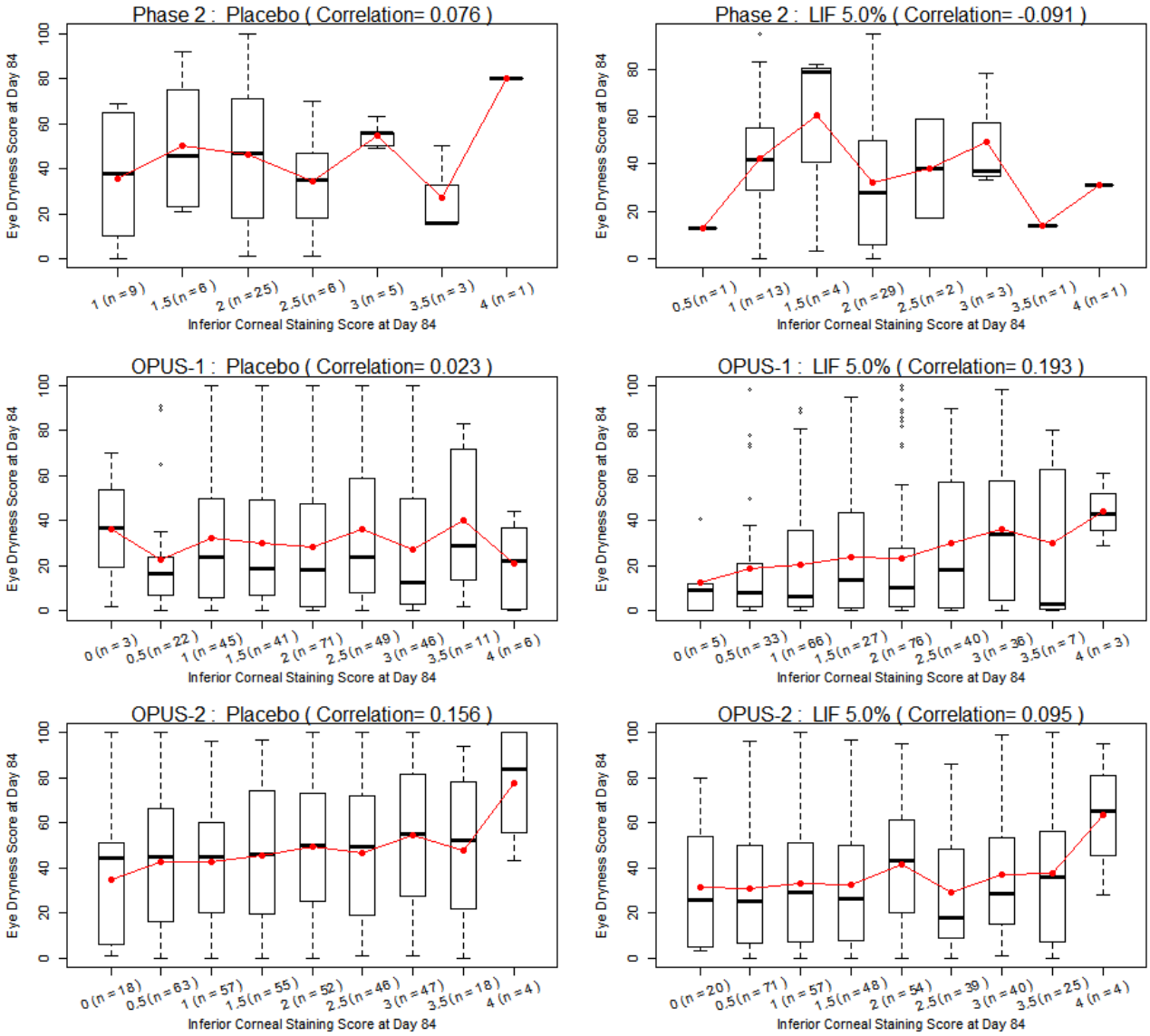
study (correlation = 0.16). However, no apparent relationship was seen between ICSS and EDS data at Day 84 in both treatment groups in the Phase 2 study, in the Placebo treated group in the OPUS-1 study, and in the LIF 5.0% treated group in the OPUS-2 study.

Figure 17: Relationship between ICSS and EDS at Day 84
(ITT Population)



<u>Meanc change in ICSS, EDS, and VR_OSDI by baseline ICSS category</u>

Furthermore, the mean changes in ICSS, EDS, and VR_OSDI score from baseline at Day 84 were summarized by baseline ICSS category (< 2.0, = 2.0, 2.0 – 3.0, and >3.0); the results based on OPUS-1 and OPUS-2 are shown in Figure 18. Note that since the maximum baseline ICSS in the OPUS-1 was <=3.0 by design, the > 3.0 category was applicable for only OPUS-2 study.

From the first raw in Figure 18, we observe that subjects with baseline ICSS < 2.0 in both studies did not show improvement in ICSS at Day 84; however, subjects with baseline ICSS ≥2.0 in LIF 5.0% treated group in both studies and in Placebo treated group in OPUS-2 study showed large improvement in ICSS at Day 84.

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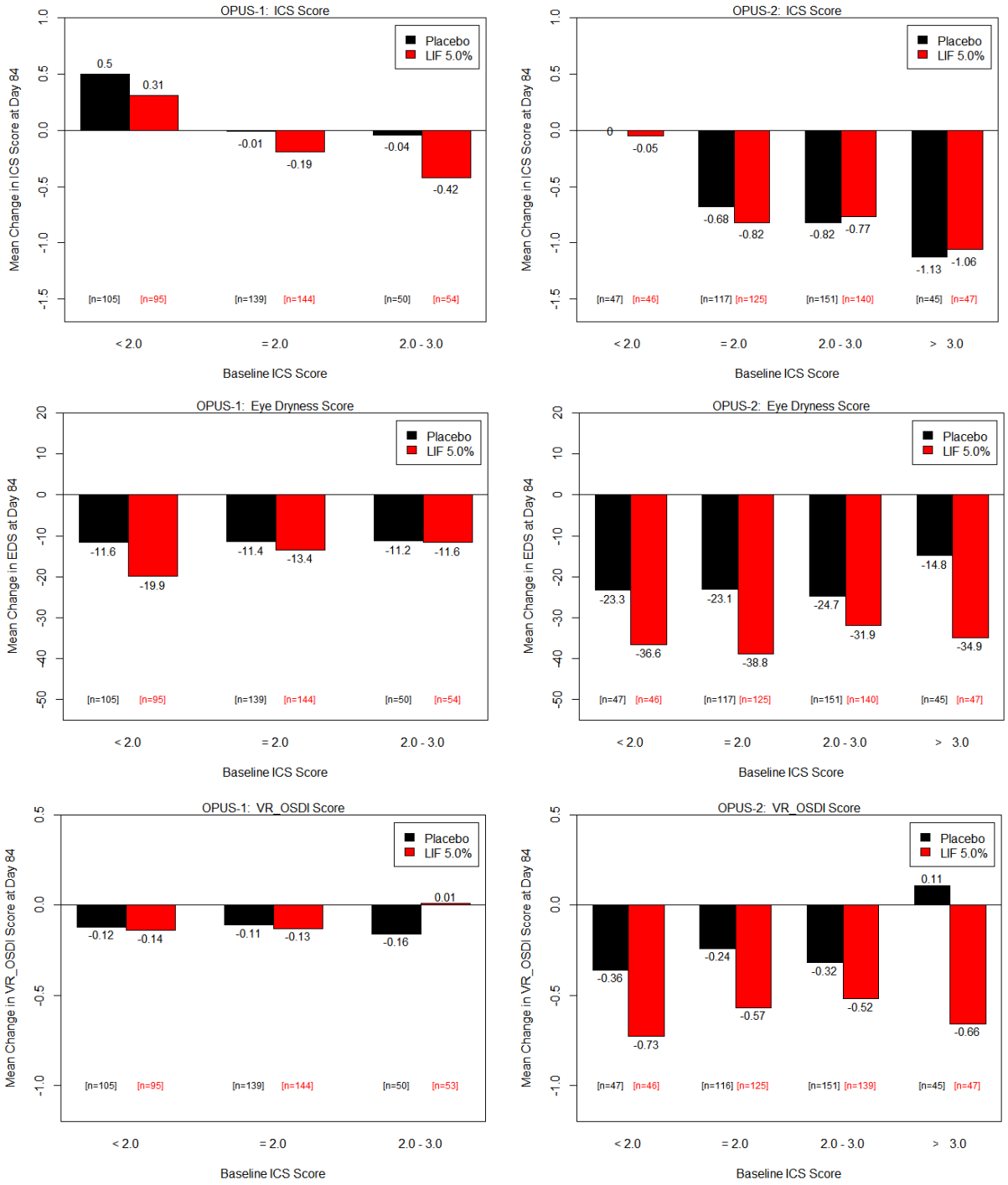
Figure 18: Mean Change in ICS, EDS, and VR_OSDI at Day 84 by Baseline ICS Category (ITT Population, LOCF)



In both studies, large mean reductions in EDS at Day 84 were observed within each of the baseline ICSS categories (see 2nd row of Figure 18); in the Placebo treated group, the mean reductions observed in each of the baseline ICSS categories were about the same in both studies whereas in LIF 5.0% treated group, subjects with baseline ICS score of ≤ 2.0 had a slightly larger mean reductions in EDS compared with subjects with baseline ICS score of > 2.0. The results for

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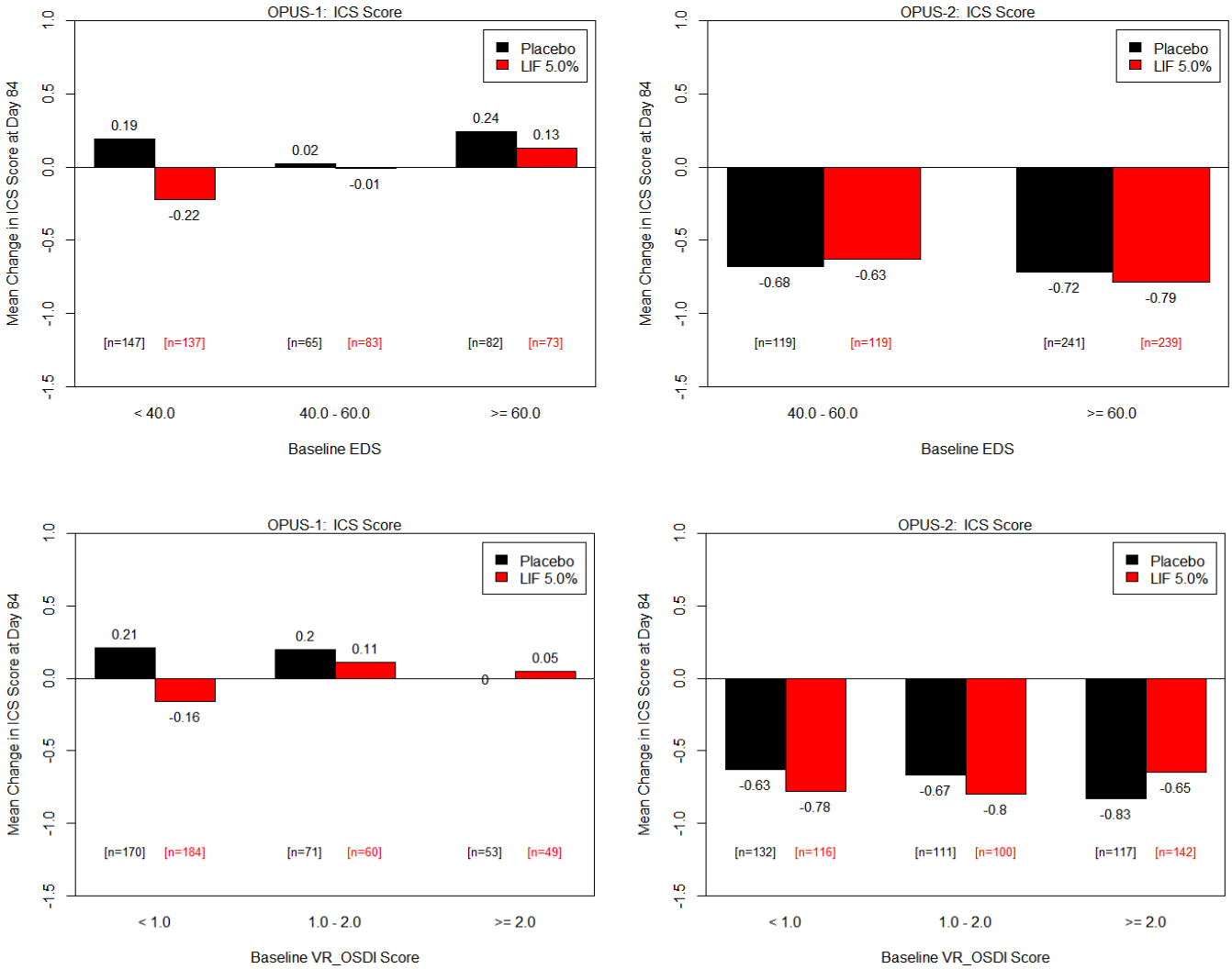
the mean reductions in VR_OSDI score at Day 84 (See Figure 18 3rd row) by baseline ICSS categories were similar to what was seen for the mean reduction in EDS.

Meanc change in ICSS by baseline EDS and VR_OSDI category

In Figure 19, the mean changes in ICSS from baseline at Day 84 were summarized by baseline EDS score category (<40.0, 40.0 - 60.0, and >= 60.0) and by baseline VR_OSDI score category (< 1.0, 1.0 - 2.0, and >= 2.0). Note that since the baseline EDS in the OPUS-2 study was ≥ 40.0 by design, the < 40.0 category is applicable only for OPUS-1 study.

Figure 19: Mean Change in ICSS at Day 84 by Baseline EDS and VR_OSDI Score Category (ITT Population, LOCF)



In subjects with baseline EDS 40 – 60 and ≥ 60 categories, both Placebo and LIF 5.0% treated groups in the OPOS-2 study demonstrated large and numerically comparable mean reductions in ICS score at Day 84 while both treatement groups in the OPUS-1 study did not show mean reductions in these categories. In subjects with baseline EDS < 40.0 in the OPUS-1 study, only LIF 5.0% treated subjects demonstrated mean reductions in ICSS at Day 84. The pattern for the mean reduction in ICSS at Day 84 by the baseline VR_OSDI categories was similar to the pattern seen by the baseline EDS cateogries.

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In summary, when the mean reductions in ICSS at Day 84 was summarized by the baseline EDS and VR_OSDI categories, clear and consistent pattern was not seen between OPUS-1 and OPUS-2 study.

Meanc change in ICSS by baseline EDS and ICSS category

The mean reduction in ICSS at Day 84 was further summarized by the combination of baseline ICSS (< 2.0, =2.0, 2.0–3.0, and >3.0) and baseline EDS (<40.0, 40.0 - 60.0, and >= 60.0) categories. The results for OPUS-1 and OPUS-2 studies are shown in Figure 20 and Figure 21.

Figure 20: Mean Change in ICSS from Baseline at Day 84 by Baseline ICSS and EDS (OPUS-1) (ITT Population, LOCF)

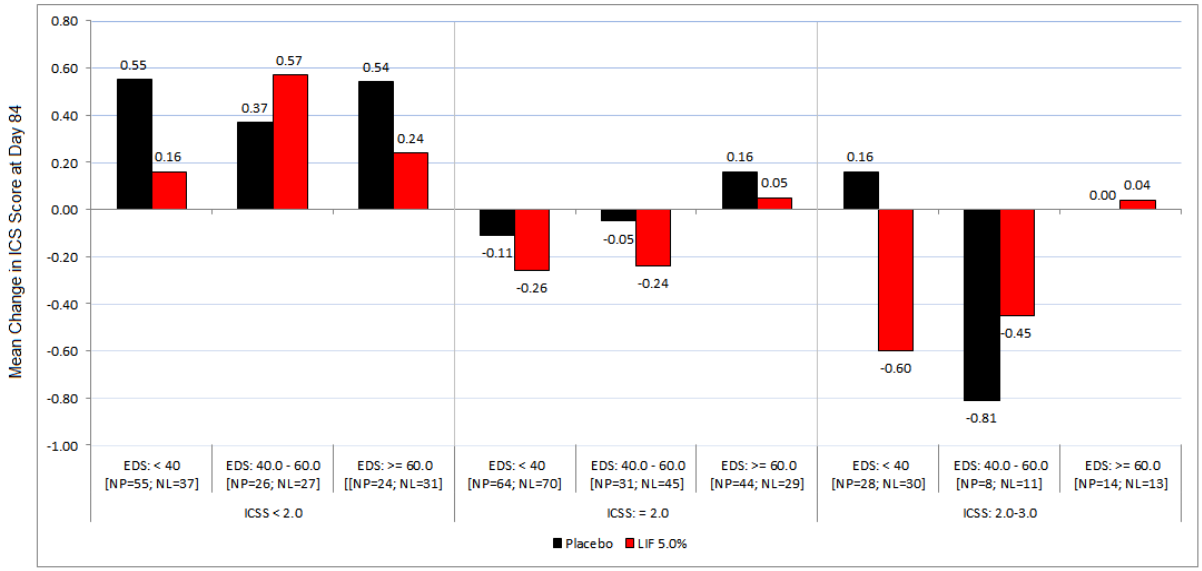
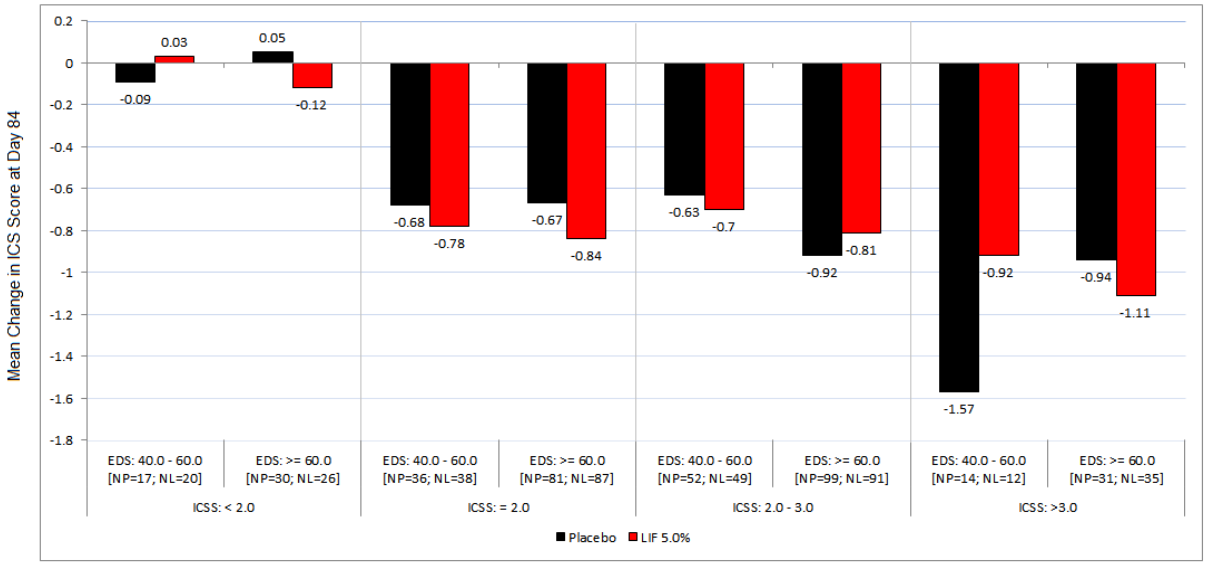


Figure 21: Mean Change in ICSS from Baseline at Day 84 by Baseline ICSS and EDS (OPUS-2) (ITT Population, LOCF)



In summary, when the mean reductions in ICSS at Day 84 was summarized by the combination of baseline ICSS and baseline EDS categories, clear and consistent pattern was not seen in OPUS-1 and OPUS-2 study.

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3.2.4.3 Secondary Efficacy Endpoints

In each study protocols, several sign and symptom secondary efficacy endpoints were defined. All the secondary efficacy variables in each study and at each time point were analyzed using the same analysis method used for the co-primary efficacy endpoints.

In the Phase 2 study, all the secondary efficacy endpoints were intended to be exploratory in nature, and hence no formal correction for multiplicity was performed across the secondary endpoints. In the OPUS-1 and OPUS-2 studies, a testing strategy was defined in the study protocols to control the Type I error rates across the secondary endpoints if both co-primary endpoints were significant. However, statistical significance was not achieved in the symptom co-primary endpoint in the OPUS-1 study and in the sign co-primary endpoint in the OPUS-2 study. Therefore, treatment comparisons for all secondary endpoints presented for these studies were considered as descriptive; that is, confidence intervals and p-values were presented as descriptive statistics without multiplicity correction.

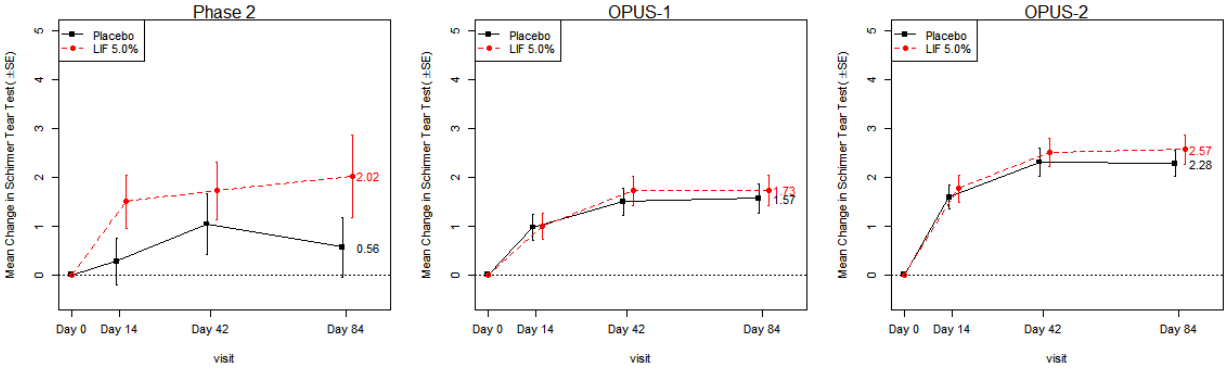
3.2.4.3.1 Mean Change in the Schirmer Tear Test (STT) Score - Sign

The schirmer tear test (without anesthesia) - an objective (sign) efficacy endpoint - measured tear production based on the length of wetting area (in mm/5 minutes). The mean STT score was defined in the Phase 2 and OPUS-1 studies as the secondary sign endpoint.

To evaluate the effectiveness of each treatment group in improving tear production, the length of wetting area was compared between the treatment groups - longer wetting area was associated with better efficacy benefit.

The mean STT score at baseline was about 5 mm in each study; the mean baseline score was balanced between the treatment groups. For each study, the mean changes in STT score from baseline at each visit are shown in Figure 22 for each study.

Figure 22: Mean Change in STT (in mm/5 minutes) Score from Baseline
(ITT Population, LOCF)



Source: Appendix Table 15

In the Phase 2 study, LIF 5.0% treated group had a larger mean increase in STT score throughout the study compared with Placebo treated group. In the OPUS-1 and OPUS-2 studies, both Placebo and LIF 5.0% treated group demonstrated large mean increase in STT score from baseline throughout the study. The mean increases at Days 42 and 84 were slightly higher in the LIF 5.0% treated group; however, a statistical significance difference was not achieved at any of the time points in all the studies (See Appendix Table 15).

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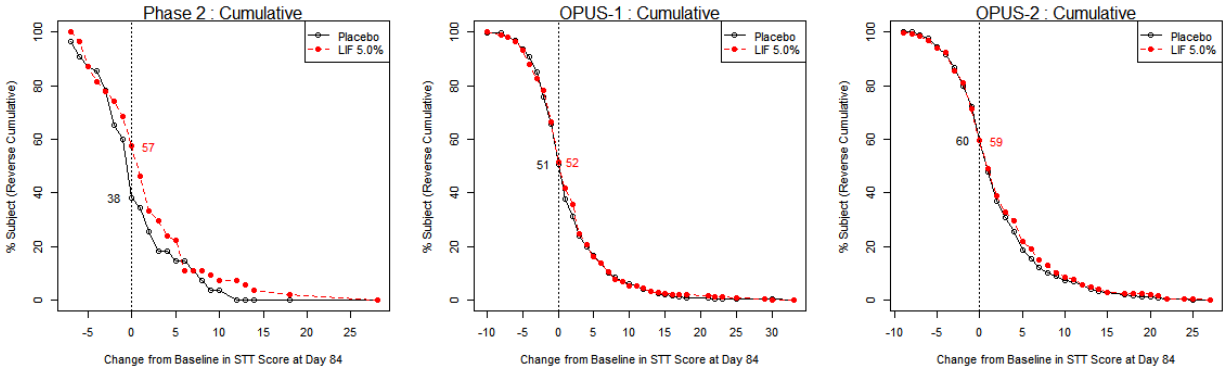
In Figure 23 below, the revers cumulative distribution for the change in STT score from baseline at Day 84 are shown. In the OPUS-1 and OPUS-2 studies, the distributions for the Placebo and LIF 5.0% treated group were indistinguishable; about 50% of subjects in each treatment group in the OPUS-1 study and about 60% of subjects in each treatment group in the OPUS-2 study showed some form of increase in STT score from baseline at Day 84. In the Phase 2 study, on the other hand, about 20% more LIF 5.0% treated subjects showed some form of increase in STT score at Day 84 compared with Placebo treated subjects.

Figure 23: Cumulative Distribution of Change in STT Score from Baseline at Day 84
(ITT Population, LOCF)



3.2.4.3.2 Mean Change in Total Corneal Staining Score (Total CSS) - Sign

Objective assessment for dry eye was also assessed using the total corneal staining scores (Total CSS). The mean change in Total CSS from baseline at Day 84 was defined in the OPUS-2 study as the secondary sign endpoint.

The Total CSS included the three regions of corneal fluorescein staining (inferior, central, and superior) where each region was scored in 0-4 scale with 0.5 increment (0 = no staining); the Total CSS was derived as the sum of the three regions (0-12 points). Note that the inferior corneal staining score (ICSS) was the primary efficacy sign endpoint in each study.

The mean Total CSS at baseline was about 4.3 in the Phase 2 study, about 4.8 in OPUS-1 study, and about 5.2 in the OPUS-2 study. The mean changes (± SE) in Total CSS from baseline at each visit are shown in Figure 24 for each study. The overall pattern for the mean change in Total CSS score over time was closely similar to the pattern observed for the mean change in ICSS over time (See Figure 9).

In each study, LIF 5.0% treated group had numerically larger mean reduction in the Total CSS at Day 84 compared with Placebo treated group; however, statistical significance difference in the mean change in Total CSS between the treatment groups was achieved in only OPUS-1 study (See Appendix Table 16).

Both treatment groups in the OPUS-2 study demonstrated larger mean reductions in Total CSS from baseline throughout the study compared with in the Phase 2 and OPUS-1 studies; however, in this study, the mean reductions between the treatment groups at Day 84 were virtually the same.

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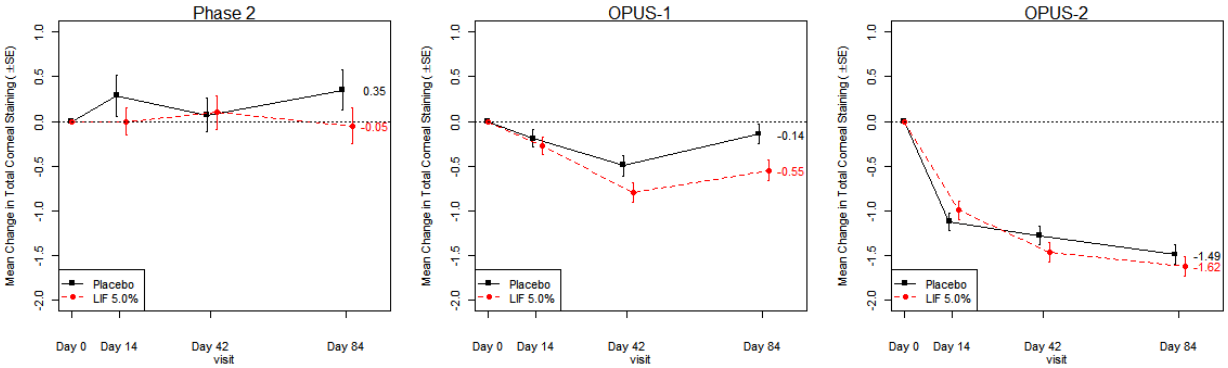
Figure 24: Mean Change in Total CSS from Baseline over Time
(ITT Population, LOCF)



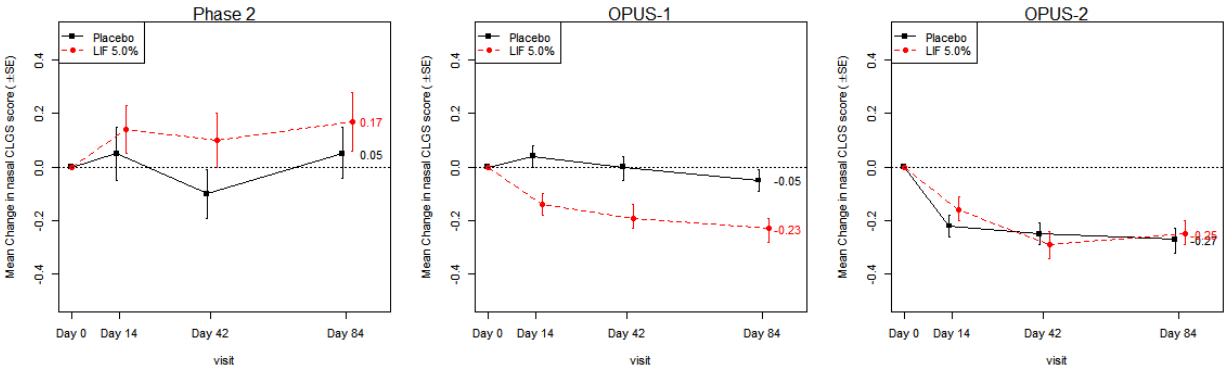
Source: Appendix Table 16

3.2.4.3.3 Mean Change in Nasal Conjunctival Lissamine Green Staining Score (Nasal CLGSS) – Sign

Objective assessment for dry eye was also assessed using Nasal CLGSS. The mean change in Nasal CLGSS from baseline at Day 84 was defined in the OPUS-2 study as the secondary sign endpoint. Similar to the corneal fluorescein staining, conjunctival lissamine green staining were also scored in 0-4 scale with 0.5 increment (0 = no staining).

The mean Nasal CLGSS at baseline was about 1.7 in the Phase 2 study, about 1.9 in OPUS-1 study, and about 2.1 in the OPUS-2 study. The mean changes (± SE) in Nasal CLGSS from baseline at each visit are shown in Figure 25 for each study.

Figure 25: Mean Change in Nasal CLGS Score from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 17

In the Phase 2 study, LIF 5.0% appeared to be less effective than Placebo in improving Nasal CLGSS; however, this may be due to slight difference in the baseline score; note that in this study, 10% more subjects in the Placebo group had baseline score > 1.5 compared with LIF 5.0%. In the OPUS-1 study, LIF 5.0% treated group appeared to be more effective in improving Nasal CLGSS throughout the study, and at each visit, statistical significant difference in the mean reduction in Nasal CLGSS was achieved between the treatment groups (See Appendix Table 17). The baseline scores in this study as well were slightly unbalanced; about 10% more subjects in the LIF 5.0% group had baseline score > 1.5 compared with in the Placebo group.

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In OPUS-2, both Placebo and LIF 5.0% groups demonstrated large and comparable mean reductions in Nasal CLGSS from baseline throughout the study. However, in this study, statistical significant difference was not achieved between the treatment groups at each visit.

3.2.4.3.4 Mean Change in Total OSDI Score – Symptom

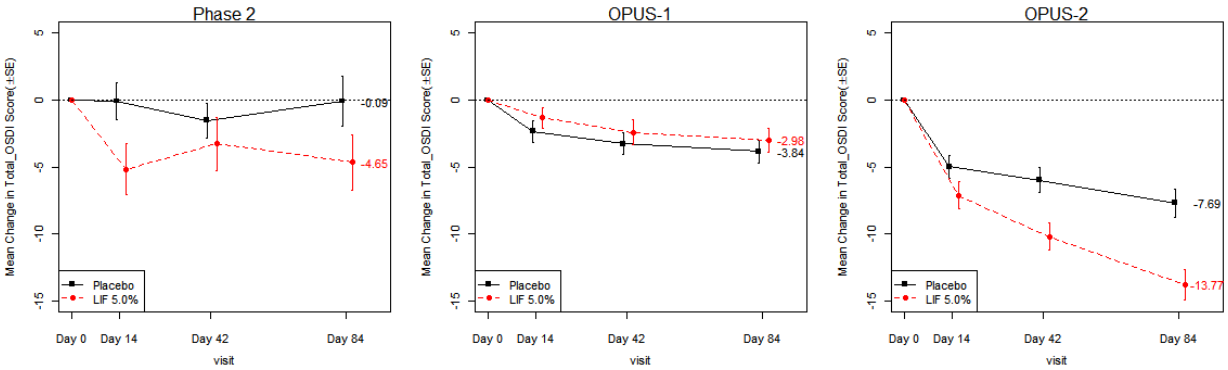
Subjective assessment for dry eye was evaluated using Total OSDI score at each visit. The mean change in Total OSDI score from baseline at Days 42 and 84 was defined in the OPUS-1 study as the secondary symptom endpoint.

The OSDI measured in 0-100 scale (0=normal, 100=sever) was derived from 12 items subject-reported questionnaire with data at each visit collected retrospectively with a 1-week recall period across both eyes. Each of the 12 items was graded in a 0-4 scale and the total score was converted to 0-100 scale. Note that the visual related OSDI subscale (VR_OSDI) was the co-primary symptom endpoint in the OPUS-1 study.

In the Phase 2 study, the mean baseline Total OSDI score in LIF 5.0% group was higher than in Placebo group by 3 units; in OPUS-1, the median baseline score in Placebo group was higher than LIF 5.0% by 2 units; the mean baseline scores in OPUS-2 study were comparable.

The mean changes (± SE) in the Total OSDI score from baseline at each visit are shown in Figure 26 by treatment group for each study. The efficacy benefit in improving Total OSDI score from baseline at each visit was compared between the treatment groups.

Figure 26: Mean Change in Total OSDI Score from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 18

In the Phase 2 study, LIF 5.0% treated group had numerically larger mean reductions in the Total OSDI score throughout the study compared with Placebo.

In the OPUS-1 study, Placebo treated group showed numerically slightly better improvement in the Total OSDI score throughout the study; however, the difference in the mean reductions between the treatment groups was very small. Note that the Placebo group in this study had slightly higher baseline score and the numerical advantage may be attributed to that.

In the OPUS-2 study, both treatment groups showed large mean reductions in Total OSDI score from baseline throughout the study; however, the mean reductions in the LIF 5.0% treated group were numerically larger than in the Placebo treated group by about 4 units at Days 42 and by about 6 units at Day 84 (See Appendix Table 18).

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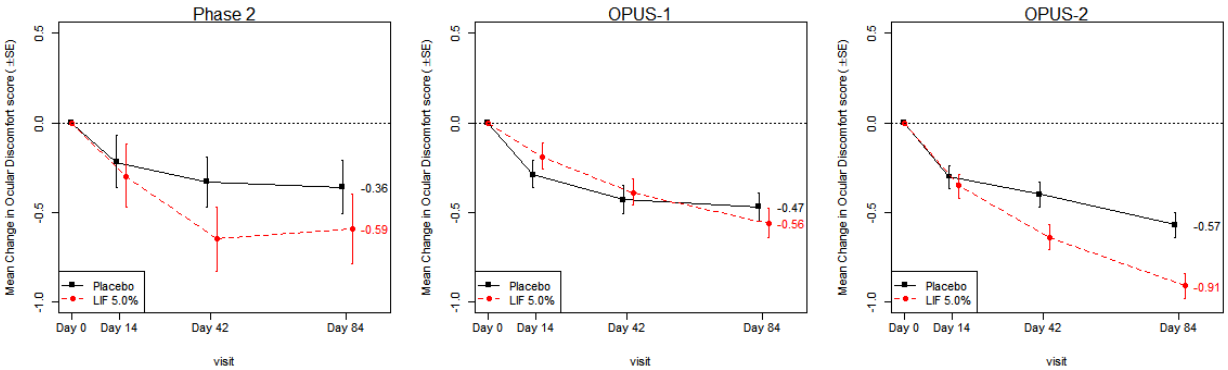
3.2.4.3.5 Mean Change in Ocular Discomfort Score (ODS) – Symptom

Subjective assessment for dry eye was also assessed using ocular discomfort score (ODS) at each visit; ODS was measured in 0–4 point scale (0=no discomfort; 4= constant discomfort). The mean change in ODS from baseline at Day 84 was defined in the OPUS-2 study as the secondary symptom endpoint.

Within each study, the mean ODS at baseline was comparable between the treatment groups; the mean baseline ODS was about 2.0 in the Phase 2 study, 1.7 in OPUS-1 study, and 2.3 in the OPUS-2 study. The mean changes (± SE) in ODS from baseline at each visit are shown in Figure 27 for each study.

Figure 27: Mean Change in ODS from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 19

In all three studies, both Placebo and LIF 5.0% treated group demonstrated mean reductions in ODS from baseline throughout the study.

In the Phase 2 and OPUS-2 studies, LIF 5.0% treated group had numerically larger mean reductions in ODS compared with Placebo treated group throughout the study; however, the Placebo treated group in OPUS-1 study had numerically slightly higher mean reductions early on while the LIF 5.0% treated group showed numerically slightly higher mean reduction at Day 84 (See Appendix Table 19).

3.2.4.3.6 Mean Change in Eye Discomfort Score (EDisS) – Symptom

Subjective assessment for dry eye was also assessed using the eye discomfort score (EDisS) of the 7-item VAS at each study visits in OPUS-2 study only; EDisS was measured in 0-100 point scale (0 = no discomfort; 100=maximum discomfort) across both eyes.

The mean EDisS at baseline was about 55 units in each treatment group. The mean changes (± SE) in EDisS from baseline at each visit are shown in Figure 28 by treatment group for each study.

Clearly, both treatment groups demonstrated large mean reductions in EDisS from baseline throughout the study; however, LIF 5.0% treated group demonstrated numerically higher mean reductions throughout the study compared with Placebo treated group. At Day 84, the mean reduction in EDisS was higher in the LIF 5.0% treated group by about 9 units (p-value < 0.0001) (See Appendix Table 20).

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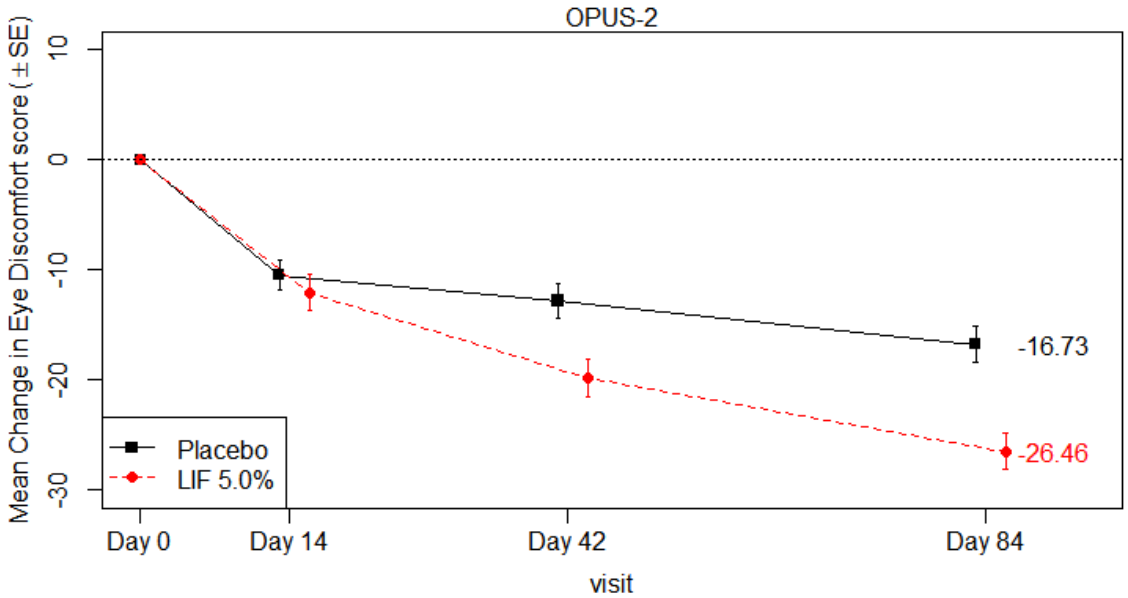
Figure 28: Mean Change in Total ODS Score from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 20

3.2.4.4 Exploratory Efficacy Endpoints

In each study, a number of exploratory sign and symptom efficacy endpoints were defined in the study specific protocols. The efficacy results for these endpoints were presented and discussed in the applicant clinical study summary reports. For the results of these exploratory endpoints, we defer to the clinical study report.

3.2.4.5 Sensitivity Analysis

In the Phase 2, OPUS-1, and OPUS-2 study, respectively, a total of 20 (17%), 23 (4%), and 49 (14%) subjects discontinued before Week 12. The discontinuation rate in each treatment group in the Phase 2 study (about 10% each) and in OPUS-1 study (about 4% each) was comparable. In the OPUS-2 study, on the other hand, the discontinuation rate in the LIF 5.0 treated group was three times higher than in the Placebo treated group (10% in the LIF 5.0% treated group versus 3% in the Placebo treated group). In all studies, the most common reason for discontinuation in the LIF 5.0% treated groups was due to adverse events.

To assess the impact on the primary analyses result of missing data due to drop-outs and to assess the robustness of the primary sign and symptom efficacy results under different data handling approaches, several sensitivity analyses were performed:

- ANCOVA analysis using observed data (without missing data imputation) and using worst observation carried forward (WOCF) for imputing missing data, and
- A mixed model repeated measure analysis (MMRM) using observed data.

The results for the primary sign and symptom efficacy endpoints and for the key secondary sign and symptom endpoints at Day 84 based on these analyses methods are shown in Appendix Table 22, Table 23, and Table 24. The results from the sensitivity analyses methods were consistent with the primary efficacy analysis approach that used LOCF method for imputing missing data .

Reference ID: 3938302

3.3 Safety evaluation

In this section a high level safety summary for the individual Phase 2, OPUS-1, OPUS-2, and SONATA study, and for the integrated safety population was provided; a comprehensive safety evaluation of the product is primarily covered in the FDA clinical review. The Phase 2, OPUS-1, and OPUS-2 studies were designed to evaluate the safety and efficacy of LIF 5.0% compared to Placebo whereas the SONATA study was specifically designed to evaluate the safety of LIF 5.0% compared to Placebo in subjects with dry eye.

The SONATA study was a Phase 3, multicenter, randomized, double–masked and placebo–controlled study. The key inclusion criteria in this study were similar to in the OPUS-2 study. In this study, a total of 332 subjects were randomized to either LIF 5.0% or Placebo (2:1) and received treatment twice daily for one year (360 days) to compare the safety profiles. In this study, a total 19 (17%) Placebo treated subjects and 50 (23%) LIF 5.0% treated subjects discontinued before one year. Adverse event (AE) was the most common reason for discontinuation in both treatment groups (about 12% in LIF 5.0% versus 8% in Placebo).

In all studies, safety was evaluated based on all randomized subjects who received at least a single dose of double blind treatment. The high level safety summary in this review included extent of exposure to study drug and adverse events (AEs).

The integrated safety population included a total of 1753 subjects; 823 subjects were included in the placebo treated group and 930 subjects were included in the LIF 5.0% treated group. Subjects included in the integrated safety population had mean age of 60 years at enrollment, most subjects were white (87%), and there were more women (76%) than men.

3.3.1 Exposure to Study Drug

The summary of exposure to study drug are shown in Table 9 below. In each study, the mean duration of exposure to study drug was numerically slightly lower in the LIF 5.0% treated group compared to the Placebo treated group whereas the median duration of exposure was comparable between the treatment groups.

Table 9: Summary of Duration of Exposure to Study Drug
(Safety Analysis Population)

	Placebo				LIF 5.0%			
Studies	N	Mean (SD)	Median	Range	N	Mean (sd)	Median	Range
Phase 2 [1]	58	80.5 (14.3)	84	13 - 95	58	75.2 (21.7)	84	14 - 91
OPUS-1 [2]	295	84.0 (7.8)	85	21 - 132	293	82.3 (11.0)	85	13 - 92
OPUS-2 [3]	359	82.1 (8.8)	85	14 - 94	359	78.2 (17.8)	85	1 - 93
SONATA [4]	111	311.3 (114.3)	359	1 - 370	220	304.4 (112.5)	359	1 - 377

Source - Clinical Study Reports: [1] Table 14.3.11; [2] Table 4.1.2; [3] Table 4.1.1; [4] Table 4.1.1

3.3.2 Adverse Events

In the combined studies, a total of 1753 subjects (823 in Placebo and 930 in LIF 5.0%) were exposed to study drug. The high level summary of treatment emergent AEs (TEAEs) by treatment group are shown in Table 10 for the individual study data and for the pooled data.

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In all studies, a higher percentage of LIF 5.0% treated subjects reported at least one TEAE compared to Placebo treated subjects. In the integrated population, at least 25% more LIF 5.0% treated subjects reported at least one TEAE compared with Placebo treated subjects. The incidences of TEAEs considered by the investigator as drug-related were also significantly higher in the LIF 5.0% treated group than in the Placebo treated group (16% in Placebo versus 49% in LIF 5.0% in the integrated population).

Table 10: Overview of Treatment Emergent Adverse Events by Treatment Group
(Safety Analysis Population)

	Phase 2		**OPUS-1**		**OPUS-2**		**SONATA**		**Pooled**	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 359)**	**LIF 5.0% (N = 359)**	**Placebo (N = 111)**	**LIF 5.0% (N = 220)**	**Placebo (N = 823)**	**LIF 5.0% (N = 930)**
Subjects with at least 1 TEAE	30 (51.7)	48 (82.8)	125 (42.4)	210 (71.7)	92 (25.6)	172 (47.9)	59 (53.2)	160 (72.7)	306 (37.2)	590 (63.4)
Ocular TEAEs	15 (25.9)	40 (69.0)	75 (25.4)	174 (59.4)	59 (16.4)	121 (33.7)	38 (34.2)	118 (53.6)	187 (22.7)	453 (48.7)
Non-ocular TEAEs	22 (37.9)	19 (32.8)	77 (26.1)	106 (36.2)	45 (12.5)	96 (26.7)	40 (36.0)	104 (47.3)	184 (22.4)	325 (35.0)
Subjects with moderate or severe TEAEs	15 (27.6)	14 (27.6)	41 (13.9)	51 (17.4)	26 (8.0))	69 (22.2)	28 (27.9)	71 (37.2)	110 (13.4)	205 (22.0)
Ocular TEAEs	1 (1.7)	8 (13.8)	8 (2.7)	21 (7.2)	12 (3.3)	37 (10.3)	11 (9.9)	33 (15.0)	32 (3.9)	99 (10.6)
Non-ocular TEAEs	15 (25.9)	8 (13.8)	34 (11.5)	30 (10.2)	17 (4.7)	43 (11.9)	20 (18.0)	49 (22.2)	86 (10.4)	130 (14.0)
Subjects with treatment-related TEAEs	14 (24.1)	39 (67.2)	51 (17.3)	172 (58.7)	41 (11.4)	142 (39.6)	27 (24.3)	104 (47.3)	133 (16.2)	457 (49.1)
Ocular TEAEs	13(22.4)	38 (65.5)	49 (16.6)	161 (54.9)	37 (10.3)	102 (28.4)	23 (20.7)	88 (40.0)	122 (14.8)	389 (41.8)
Non-ocular TEAEs	2 (3.5)	7 (12.1)	6 (2.0)	47 (16.0)	6 (1.7)	70 (19.5)	6 (5.4)	41 (18.6)	20 (2.4)	165 (17.7)
Subjects prematurely withdrawn due to TEAEs	5 (8.6)	6 (10.3)	3 (1.0)	8 (2.7)	3 (0.8)	26 (7.2)	10 (9.0)	27 (12.3)	21 (2.6)	67 (7.2)
Ocular TEAEs	2 (3.4)	6 (10.3)	2 (0.7)	6 (2.1)	2 (0.6)	23 (6.4)	6 (5.4)	18 (8.2)	12 (1.5)	53 (5.7)
Non-ocular TEAEs	3 (5.2)	0 (0.0)	1 (0.7)	2 (0.3)	1 (0.3)	6 (1.7)	4 (3.6	9 (4.1)	9 (1.1)	17 (1.8)
Subjects with serious TEAEs	1 (1.7)	0 (0.0)	2 (0.7)	5 (1.7)	4 (1.1)	3 (0.8)	6 (5.4)	9 (4.1)	13 (1.6)	17 (1.8)
Ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular TEAEs	1 (1.7)	0 (0.0)	2 (0.7)	5 (1.7)	4 (1.1)	3 (0.8)	6 (5.4)	9 (4.1)	13 (1.6)	17 (1.8)
Subjects with TEAEs resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)
Ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)

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The summary of ocular TEAEs occurring in ≥1% of subjects in either treatment group based on the pooled study are presented in Table 11. The overall incidence of ocular TEAE was significantly larger in the LIF 5.0% treated group than in the Placebo treated group (23% in Placebo versus 49% in LIF 5.0% in the integrated population). The most frequent ocular TEAE in the LIF 5.0% treated group were instillation site irritation (16% versus 3% in Placebo), instillation site pain (11% versus 2% in Placebo) and instillation site reaction (12% versus 1% in Placebo).

Table 11: Ocular TEAEs Occurring in ≥1% of Subjects in either Treatment Group in the Pooled Study (Integrated Analysis; SAF)

	Phase 2		**OPUS-1**		**OPUS-2**		**SONATA**		**Pooled**	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 359)**	**LIF 5.0% (N = 359)**	**Placebo (N = 111)**	**LIF 5.0% (N = 220)**	**Placebo (N = 823)**	**LIF 5.0% (N = 930)**
Subjects with at least 1 Ocular TEAE	**15 (25.9%)**	**40 (69.0%)**	**75 (25.4%)**	**174 (59.4%)**	**59 (16.4%)**	**121 (33.7)**	**38 (34.2%)**	**118 (53.6)**	**187 (22.7%)**	**453 (48.7%)**
Eye Disorders	**9 (15.5%)**	**10 (17.2%)**	**47 15.9%)**	**55 (18.8%)**	**47 (13.1%)**	**85 (23.7%)**	**33 (29.7%)**	**82 (37.3%)**	**136 (16.5%)**	**232 (24.9%)**
Visual Acuity Reduced	3 (5.2%)	1 (1.7%)	15 (5.1%)	14 (4.8%)	23 (6.4%)	18 (5.0%)	7 (6.4%)	25 (11.4%)	48 (5.8%)	58 (6.2%)
Vision Blurred	1 (1.7%)	0 (0.0%)	3 (1.0%)	3 (1.0%)	2 (0.6%)	10 (2.8%)	4 (3.6%)	9 (4.1%)	10 (1.2%)	22 (2.4%)
Lacrimation Increased	0 (0.0%)	2 (3.4%)	1 (0.3%)	7 (2.4%)	1 (0.3%)	9 (2.5%)	2 (1.8%)	8 (3.6%)	4 (0.5%)	26 (2.8%)
Eye Irritation	0 (0.0%)	0 (0.0%)	3 (1.0%)	4 (1.4%)	1 (0.3%)	11 (3.1%)	1 (0.9%)	8 (3.6%)	5 (0.6%)	23 (2.5%)
Eye Pruritus	1 (1.7%)	0 (0.0%)	2 (0.7%)	5 (1.7%)	4 (1.1%)	4 (1.1%)	2 (1.8%)	8 (3.6%)	9 (1.1%)	17 (1.8%)
Eye Pain	0 (0.0%)	1 (1.7%)	5 (1.7%)	6 (2.0%)	1 (0.3%)	5 (1.4%)	0 (0.0%)	7 (3.2%)	6 (0.7%)	19 (2.0%)
Ocular Hyperaemia	0 (0.0%)	2 (3.4%)	4 (1.4%)	7 (2.4%)	2 (0.6%)	4 (1.1%)	0 (0.0%)	4 (1.8%)	6 (0.7%)	17 (1.8%)
Conjunctival Hyperaemia	1 (1.7%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	4 (1.1%)	5 (1.4%)	4 (3.6%)	6 (2.7%)	10 (1.2%)	12 (1.3%)
Dry Eye	1 (1.7%)	1 (1.7%)	2 (0.7%)	0 (0.0%)	2 (0.6%)	2 (0.6%)	6 (5.5%)	4 (1.8%)	11 (1.3%)	7 (0.8%)
Conjunctival Haemorrhage	0 (0.0%)	3 (5.2%)	2 (0.7%)	2 (0.7%)	1 (0.3%)	4 (1.1%)	1 (0.9%)	1 (0.5%)	4 (0.5%)	10 (1.1%)
General Disorders And Administration Site Conditions	**9 (15.5%)**	**37 (63.8%)**	**28 (9.5%))**	**142 (48.5%)**	**11 (3.1%)**	**57 (15.9%)**	**7 (6.3%)**	**51 (23.2%)**	**55 (6.7%)**	**287 (30.9%)**
Instillation Site Irritation	6 (10.3%)	20 (34.5%)	12 (4.1%)	69 (23.5%)	5 (1.4%)	28 (7.8%)	5 (4.5%)	33 (15.0%)	28 (3.4%)	150 (16.1%)
Instillation Site Pain	3 (5.2%)	20 (34.5%)	11 (3.7%)	63 (21.5%)	3 (0.8%)	11 (3.1%)	2 (1.8%)	7 (3.2%)	19 (2.3%)	101 (10.9%)
Instillation Site Reaction	0 (0.0%)	8 (13.8%)	2 (0.7%)	50 (17.1%)	4 (1.1%)	25 (7.0%)	2 (1.8%)	29 (13.2%)	8 (1.0%)	112 (12.0%)
Instillation Site Pruritus	0 (0.0%)	2 (3.4%)	6 (2.0%)	19 (6.5%)	0 (0.0%)	8 (2.2%)	1 (0.9%)	5 (2.3%)	7 (0.9%)	34 (3.7%)
Instillation Site Lacrimation	0 (0.0%)	1 (1.7%)	1 (0.3%)	7 (2.4%)	0 (0.0%)	1 (0.3%)	1 (0.9%)	3 (1.4%)	2 (0.2%)	12 (1.3%)

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Instillation Site Foreign Body Sensation	0 (0.0%)	2 (3.4%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.8%)	0 (0.0%)	6 (2.7%)	2 (0.2%)	11 (1.2%)

Reviewer Analysis

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

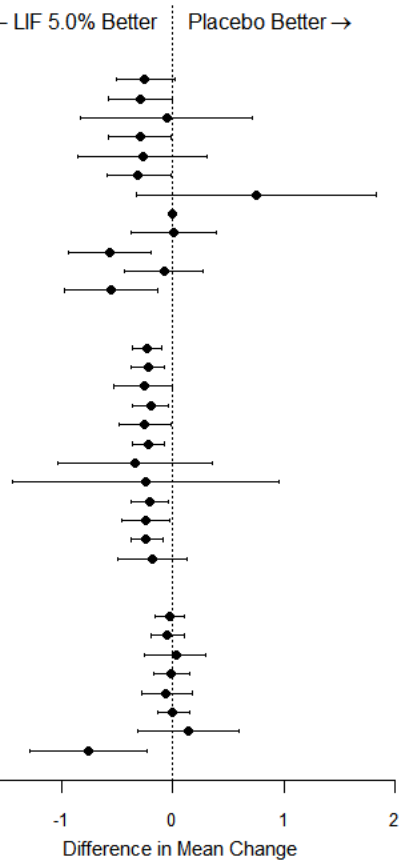
In each study, the co-primary clinical sign and symptom efficacy endpoints were analyzed by the subgroup of age, sex, race, and history of ATU using the primary efficacy analysis approach. Note that all subjects in OPUS-2 study had a history of artificial tear use (ATU).

Using ANCOVA analysis: the least square mean estimates (SE) for each treatment group, and the treatment differences (dots) with 95% confidence interval estimates (horizontal bars) by the subgroups are shown in Figure 29 for the mean change in ICSS, in Figure 30 for the mean change in VR_OSDI score, and in Figure 31 for the mean change in EDS.

The co-primary efficacy results within the levels of each of the subgroup variables were consistent with those seen in the overall population. In some subgroups there were only small number of subjects, and the results for these subgroups may not be indicative of the overall treatment effects.

Figure 29: Mean Change (±SE) in ICSS from Baseline at Day 84 by Subgroup (ITT Population, LOCF)

	Placebo		LIF 5.0%		
Phase 2 Study	**N**	**LSM (SE)**	**N**	**LSM (SE)**	**Difference (95% CI)**
Overall : Overall	55	0.35 (0.093)	54	0.10 (0.094)	-0.25 (-0.51, 0.02)
Sex : Female	44	0.35 (0.101)	44	0.07 (0.101)	-0.29 (-0.58, -0.00)
Sex : Male	11	0.31 (0.253)	10	0.26 (0.265)	-0.05 (-0.83, 0.72)
Age : <65	38	0.26 (0.099)	34	-0.04 (0.104)	-0.29 (-0.58, -0.01)
Age : >=65	17	0.58 (0.203)	20	0.31 (0.186)	-0.27 (-0.86, 0.31)
Race : White	51	0.40 (0.099)	49	0.10 (0.101)	-0.31 (-0.59, -0.02)
Race : Black or African American	3	-0.50 (0.150)	2	0.25 (0.187)	0.75 (-0.33, 1.83)
Race : Other	1	0.00 (NA)	3	0.00 (NA)	0.00 (NA , NA)
Artificial Tear Use : No	26	0.12 (0.134)	26	0.13 (0.134)	0.01 (-0.37, 0.39)
Artificial Tear Use : Yes	29	0.60 (0.127)	28	0.03 (0.130)	-0.57 (-0.94, -0.19)
ATU & EDS>=40 : No	33	0.21 (0.121)	30	0.13 (0.127)	-0.08 (-0.43, 0.27)
ATU & EDS>=40 : Yes	22	0.58 (0.145)	24	0.03 (0.139)	-0.56 (-0.97, -0.14)
OPUS-1 Study					
Overall : Overall	294	0.16 (0.047)	293	-0.07 (0.047)	-0.23 (-0.36, -0.10)
Sex : Female	216	0.15 (0.056)	229	-0.07 (0.054)	-0.22 (-0.38, -0.07)
Sex : Male	78	0.20 (0.089)	64	-0.06 (0.098)	-0.26 (-0.53, 0.00)
Age : <65	177	0.15 (0.059)	194	-0.05 (0.056)	-0.20 (-0.36, -0.04)
Age : >=65	117	0.17 (0.079)	99	-0.08 (0.086)	-0.25 (-0.48, -0.02)
Race : White	275	0.16 (0.049)	270	-0.06 (0.049)	-0.22 (-0.36, -0.08)
Race : Black or African American	11	0.06 (0.255)	16	-0.29 (0.209)	-0.34 (-1.04, 0.36)
Race : Other	8	0.41 (0.356)	7	0.17 (0.381)	-0.24 (-1.44, 0.96)
Artificial Tear Use : No	166	0.17 (0.059)	165	-0.04 (0.059)	-0.21 (-0.37, -0.04)
Artificial Tear Use : Yes	128	0.15 (0.076)	128	-0.09 (0.076)	-0.24 (-0.46, -0.03)
ATU & EDS >= 40 : No	227	0.14 (0.052)	230	-0.09 (0.052)	-0.24 (-0.38, -0.09)
ATU & EDS >= 40 : Yes	67	0.21 (0.108)	63	0.03 (0.111)	-0.18 (-0.49, 0.13)
OPUS-2 Study					
Overall : Overall	360	-0.70 (0.047)	358	-0.74 (0.047)	-0.03 (-0.16, 0.10)
Sex : Female	265	-0.71 (0.055)	285	-0.76 (0.053)	-0.05 (-0.20, 0.10)
Sex : Male	95	-0.67 (0.092)	73	-0.65 (0.105)	0.03 (-0.25, 0.30)
Age : <65	225	-0.76 (0.058)	236	-0.77 (0.057)	-0.01 (-0.17, 0.15)
Age : >=65	135	-0.61 (0.079)	122	-0.67 (0.083)	-0.06 (-0.28, 0.17)
Race : White	305	-0.73 (0.051)	303	-0.72 (0.051)	0.00 (-0.14, 0.15)
Race : Black or African American	34	-0.89 (0.149)	30	-0.75 (0.159)	0.14 (-0.31, 0.59)
Race : Other	21	-0.11 (0.188)	25	-0.87 (0.171)	-0.76 (-1.29, -0.23)



LSM: Least Square Mean; SE: Standard Error; LIF 5.0%: Lifitegrast Ophthalmic Solution 5.0%.
LSM (SE) were derived from ANCOVA model that adjusted for the baseline ICS score in the phase 2 study and for the baseline and stratification factors in the OPUS-1 and OPUS-2 studies.
ATU: Artifical Tear Use; EDS: Eye Dryness Score

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Note that in the subgroup of patients with a history of ATU in the Phase 2 study, LIF 5.0% showed numerically larger reduction in ICSS compared with Placebo; in this subgroup, the treatment difference was -0.57 (95% CI: -0.94, -0.19).

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Figure 30: Mean Change (±SE) in VR_OSDI from Baseline at Day 84 by Subgroup
(ITT Population, LOCF)

Phase 2 Study	Placebo N	Placebo LSM (SE)	LIF 5.0% N	LIF 5.0% LSM (SE)	Difference (95% CI)
Overall : Overall	55	0.03 (0.116)	54	-0.27 (0.117)	-0.30 (-0.63, 0.03)
Sex : Female	44	0.04 (0.130)	44	-0.15 (0.130)	-0.19 (-0.56, 0.18)
Sex : Male	11	-0.03 (0.239)	10	-0.71 (0.251)	-0.67 (-1.40, 0.06)
Age : <65	38	0.01 (0.144)	34	-0.26 (0.152)	-0.27 (-0.69, 0.15)
Age : >=65	17	0.08 (0.191)	20	-0.28 (0.176)	-0.36 (-0.89, 0.17)
Race : White	51	-0.05 (0.118)	49	-0.24 (0.121)	-0.18 (-0.52, 0.15)
Race : Black or African American	3	1.46 (1.081)	2	-0.94 (1.551)	-2.39 (-13.09, 8.31)
Race : Other	1	0.38 (0.187)	3	-0.46 (0.104)	-0.84 (-3.62, 1.95)
Artificial Tear Use : No	26	0.26 (0.177)	26	-0.32 (0.177)	-0.58 (-1.09, -0.08)
Artificial Tear Use : Yes	29	-0.20 (0.150)	28	-0.18 (0.153)	0.02 (-0.42, 0.45)
OPUS-1 Study					
Overall : Overall	295	-0.11 (0.039)	292	-0.12 (0.039)	-0.01 (-0.12, 0.10)
Sex : Female	217	-0.12 (0.046)	228	-0.16 (0.045)	-0.04 (-0.17, 0.08)
Sex : Male	78	-0.06 (0.075)	64	-0.01 (0.083)	0.05 (-0.17, 0.27)
Age : <65	178	-0.19 (0.050)	193	-0.17 (0.048)	0.02 (-0.12, 0.16)
Age : >=65	117	0.00 (0.063)	99	-0.02 (0.068)	-0.02 (-0.21, 0.16)
Race : White	276	-0.09 (0.040)	269	-0.12 (0.040)	-0.04 (-0.15, 0.07)
Race : Black or African American	11	-0.48 (0.199)	16	-0.12 (0.163)	0.37 (-0.18, 0.91)
Race : Other	8	-0.36 (0.443)	7	-0.03 (0.475)	0.32 (-1.17, 1.81)
Artificial Tear Use : No	166	-0.12 (0.052)	165	-0.12 (0.053)	0.00 (-0.14, 0.15)
Artificial Tear Use : Yes	129	-0.09 (0.059)	127	-0.12 (0.059)	-0.03 (-0.20, 0.13)
OPUS-2 Study					
Overall : Overall	359	-0.28 (0.048)	357	-0.55 (0.048)	-0.28 (-0.41, -0.14)
Sex : Female	265	-0.26 (0.056)	284	-0.55 (0.055)	-0.29 (-0.44, -0.13)
Sex : Male	94	-0.31 (0.090)	73	-0.58 (0.102)	-0.27 (-0.54, 0.00)
Age : <65	224	-0.29 (0.060)	236	-0.59 (0.059)	-0.30 (-0.47, -0.13)
Age : >=65	135	-0.26 (0.080)	121	-0.49 (0.085)	-0.23 (-0.46, -0.00)
Race : White	304	-0.28 (0.052)	302	-0.53 (0.052)	-0.26 (-0.40, -0.11)
Race : Black or African American	34	-0.55 (0.162)	30	-0.84 (0.173)	-0.29 (-0.78, 0.20)
Race : Other	21	0.11 (0.204)	25	-0.40 (0.186)	-0.51 (-1.09, 0.06)

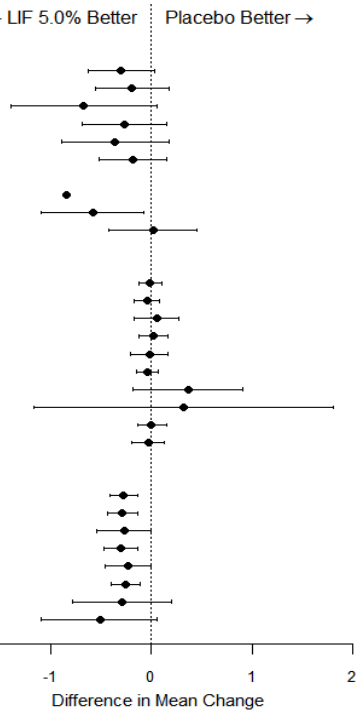
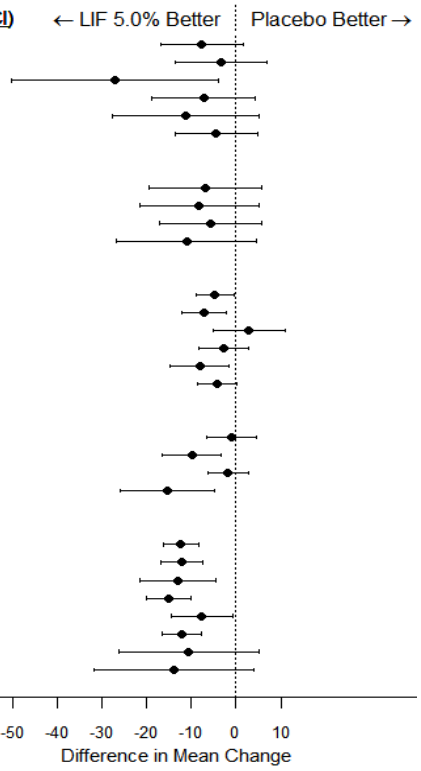


Figure 31: Mean Change (±SE) in EDS from Baseline at Day 84 by Subgroup
(ITT Population, LOCF)

Phase 2 Study	Placebo N	Placebo LSM (SE)	LIF 5.0% N	LIF 5.0% LSM (SE)	Difference (95% CI)
Overall : Overall	55	-7.70 (3.240)	53	-15.33 (3.301)	-7.63 (-16.80, 1.54)
Sex : Female	44	-10.46 (3.592)	43	-13.79 (3.633)	-3.33 (-13.49, 6.84)
Sex : Male	11	4.19 (7.420)	10	-22.91 (7.797)	-27.10 (-50.14, -4.06)
Age : <65	38	-8.91 (3.952)	33	-16.11 (4.242)	-7.20 (-18.79, 4.39)
Age : >=65	17	-3.78 (5.884)	20	-15.08 (5.413)	-11.30 (-27.76, 5.16)
Race : White	51	-9.95 (3.198)	48	-14.33 (3.297)	-4.38 (-13.50, 4.74)
Race : Black or African American	3	22.58 (7.829)	2	-48.87 (9.830)	-71.45 (NA, NA)
Race : Other	1	49.90 (119.13)	3	-20.30 (49.065)	-70.19 (NA, NA)
Artificial Tear Use : No	26	-2.90 (4.423)	25	-9.78 (4.511)	-6.89 (-19.59, 5.82)
Artificial Tear Use : Yes	29	-12.05 (4.678)	28	-20.23 (4.761)	-8.18 (-21.57, 5.20)
ATU & EDS >=40 : No	33	-2.63 (3.888)	29	-8.25 (4.148)	-5.62 (-17.0, 5.76)
ATU & EDS >=40 : Yes	22	-14.0 (5.614)	24	-25.1 (5.371)	-11.10 (-26.9, 4.68)
OPUS-1 Study					
Overall : Overall	295	-10.86 (1.530)	293	-15.55 (1.536)	-4.68 (-8.94, -0.43)
Sex : Female	217	-9.99 (1.839)	229	-17.17 (1.790)	-7.19 (-12.23, -2.14)
Sex : Male	78	-13.02 (2.689)	64	-10.07 (2.970)	2.95 (-4.99, 10.89)
Age : <65	178	-12.00 (2.058)	194	-14.71 (1.971)	-2.71 (-8.32, 2.90)
Age : >=65	117	-9.09 (2.259)	99	-17.22 (2.459)	-8.13 (-14.77, -1.50)
Race : White	276	-11.23 (1.564)	270	-15.44 (1.581)	-4.21 (-8.58, 0.16)
Race : Black or African American	11	2.63 (8.064)	16	-24.87 (6.633)	-27.50 (-49.66, -5.34)
Race : Other	8	-8.74 (12.527)	7	-7.73 (13.417)	1.01 (-41.09, 43.11)
Artificial Tear Use (ATU) : No	166	-12.61 (1.999)	165	-13.49 (2.005)	-0.89 (-6.46, 4.68)
Artificial Tear Use (ATU) : Yes	129	-8.47 (2.365)	128	-18.35 (2.375)	-9.88 (-16.49, -3.27)
ATU and EDS >= 40 : No	228	-7.98 (1.650)	230	-9.71 (1.643)	-1.73 (-6.31, 2.85)
ATU and EDS >= 40 : Yes	67	-21.1 (3.699)	63	-36.4 (3.816)	-15.3 (-25.9, -4.71)
OPUS-2 Study					
Overall : Overall	360	-22.86 (1.450)	358	-35.19 (1.454)	-12.33 (-16.36, -8.30)
Sex : Female	265	-23.58 (1.700)	285	-35.78 (1.639)	-12.20 (-16.84, -7.56)
Sex : Male	95	-20.38 (2.822)	73	-33.47 (3.224)	-13.09 (-21.60, -4.59)
Age : <65	225	-20.12 (1.801)	236	-35.11 (1.759)	-14.98 (-19.93, -10.03)
Age : >=65	135	-27.55 (2.427)	122	-35.20 (2.553)	-7.65 (-14.61, -0.70)
Race : White	305	-23.18 (1.565)	303	-35.23 (1.570)	-12.06 (-16.41, -7.70)
Race : Black or African American	34	-24.12 (5.173)	30	-34.67 (5.531)	-10.55 (-26.23, 5.12)
Race : Other	21	-19.03 (6.286)	25	-32.90 (5.719)	-13.87 (-31.75, 4.01)



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5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES

There are no major statistical issues identified in this submission. The following are minor data and analysis issues identified during the review:

iii) Data Issue

In the OPUS-2 study, randomization was stratified by baseline ICSS (≤1.5 versus >1.5) and baseline EDS (≤ 60 versus > 60). The following issues were identified during review of the data:

- A total of 23 subjects (11 in Placebo and 13 in LIF 5.0%) with baseline ICSS > 1.5 were incorrectly categorized as having baseline ICSS ≤ 1.5.
- Eleven subjects (6 in Placebo and 5 in LIF 5.0%) with baseline ICSS <=1.5 were incorrectly categorized as having baseline ICSS > 1.5.
- Eleven subjects (5 in Placebo and 6 in LIF 5.0%) with baseline EDS ≥ 60 were incorrectly categorized as having baseline EDS < 60.
- Four subjects (2 in each treatment group) with baseline EDS < 60 were incorrectly classified as having baseline EDS ≥ 60.

The overall efficacy conclusion remained the same when all analyses using the corrected stratification variable were performed.

iv) Analysis Issue

The applicant primary efficacy analysis approach used in the Phase 2, OPUS-1 and OPUS-2 studies were different. In the Phase 2 study, ANCOVA analysis was used to compare the treatment groups in the primary sign and symptom endpoints; in OPUS-1 study, a two-sample t-test was used; and in OPUS-2 study, a regression (ANOVA) analysis was performed. The applicant primary analyses except in the Phase 2 study did not adjust for the baseline values. Furthermore, the three studies differed in the efficacy endpoint definition: the primary sign endpoint in the Phase 2 study was based on the actual ICSS at Day 84 whereas in the OPUS-1 and in the OPUS-2 studies were based on the change from baseline in ICSS at Day 84.

Therefore, for ease of across study assessment, the statistical reviewer primary analysis approach (for all the studies) used ANCOVA model. In the model, the change from baseline value at Day 84 was used as the response variable, and treatment, baseline value, and the study specific strata (specific for OPUS-1 and OPUS-2) was used as covariates. Note that using the actual or the change from baseline value as a response variable in the ANCOVA model provides the same results for treatment comparison.

Based on the ANCOVA model, the difference in the mean change between the treatment groups was determined using the Least Square Means (LS Means). The default observed margin (OM) option in the LSMEANS statement of the PROC MIXED procedure in SAS was used to account for any imbalance in sample size and in the mean change values across strata.

Furthermore, the statistical reviewer performed unadjusted analyses using the two sample t-test and the non-parametric Wilcoxon rank sum test as sensitivity analysis.

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5.2 COLLECTIVE EVIDENCE

Efficacy evidence to support the superiority of lifitegrast ophthalmic solution 5.0% (LIF 5.0%) administered to the ocular surface as a single drop twice daily to Placebo was based on a Phase 2 dose-ranging study and two pivotal Phase 3 trials (OPUS-1 and OPUS-2). In the Phase 3 studies, co-primary efficacy endpoints were defined for the clinical sign and clinical symptom of dry eye, and a primary clinical sign endpoint was defined in the Phase 2 study. Each study was 14 weeks in duration with 5 study visits and the co-primary endpoints were evaluated at Week 12 (Day 84). The co-primary clinical sign endpoint in each study was the mean change in ICSS from baseline at Day 84. The co-primary clinical symptom endpoint in OPUS-1 study was the mean change in VR_OSDI score from baseline at Day 84 and in OPUS-2 study was the mean change in EDS from baseline at Day 84.

In each study, the treatment differences (*LIF 5.0% minus Placebo*) in the mean changes in ICSS, VR_OSDI, and in EDS were tested using ANCOVA model. In the model, the change from baseline value at Day 84 was used as the response variable, and treatment, baseline value, and the study specific strata (specific for OPUS-1 and OPUS-2) were used as covariates.

Sign Endpoint: Inferior Corneal Staining Score (ICSS):

The change in ICSS from baseline at Day 84 was the primary sign endpoint in each study. Statistical superiority in improving the clinical sign (as measured using ICSS) was demonstrated in OPUS-1 study. On the other hand, LIF 5.0% treated group in the Phase 2 and OPUS-2 studies did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

In OPUS-1 study, LIF 5.0% treated group showed numerically larger mean reduction in ICSS from baseline at Day 84 compared with Placebo treated group, and the treatment difference in the mean change in ICSS at Day 84 was -0.23 (95% CI: - 0.36, -0.09). Statistical significant difference was achieved between the treatment groups (p-value = 0.0007).

In the Phase 2 study, both LIF 5.0% and Placebo treated group did not show mean reduction in ICSS from baseline throughout the study; however, a dose response in the mean change in ICSS was seen at Day 84 (See Figure 9). In this study, the treatment difference in the mean change in ICSS at Day 84 was -0.25 (95% CI: -0.51, 0.02) and not statistically significant (p-value =0.0666). Though not statistically significant, the magnitude of treatment difference seen in this study (-0.25) was very close to what was seen in OPUS-1 study (-0.23); the non-statistical significance result in the Phase 2 study was likely due to smaller sample size compared with OPUS-1 study (note that the p-value in the Phase 2 study was very close to the 5% significance level).

In the OPUS-2 study, both treatment groups showed numerically larger mean reductions in ICSS throughout the study compared with in the Phase 2 and OPUS-1 studies. In this study, the treatment difference in the mean change in ICSS at Day 84 was -0.03 (95% CI: - 0.16, 0.10) and not statistically significant (p-value = 0.6122). It should be noted that the larger mean reduction in ICSS observed in both treatment groups in OPUS-2 study compared with in the Phase 2 and OPUS-1 studies was because of the larger mean baseline score in OPUS-2 study than in the Phase 2 and OPUS-1 studies, and the lack of treatment difference in OPUS-2 study (in subjects with moderate-to-sever symptom) may be attributed to insufficient study duration. Note that the mean baseline ICSS in the Phase 2 and OPUS-1 studies and the mean ICSS at Day 84 in the

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OPUS-2 study (after treatment was received for 84 days) were comparable (See Table 4). Therefore, in order to see any separation between the treatment groups in OPUS-2 study that was seen in the Phase 2 and OPUS-1 studies, longer study duration may be needed.

Symptom Endpoint: Visual-related function subscale of OSDI score (VR_OSDI)

The change in VR_OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study and was supportive symptom endpoint in the Phase 2 and OPUS-2 studies; thus, confidence intervals and p-values reported in the Phase 2 and OPUS-2 studies were intended for descriptive use.

Statistical superiority in improving clinical symptom (using VR_OSDI score) at Day 84 was not demonstrated in OPUS-1 study. LIF 5.0% treated subjects in OPUS-2 study demonstrated a much larger improvement in VR_OSDI over Placebo while in the Phase 2 study showed amoderate improvement over Placebo.

In OPUS-2 study, LIF 5.0% treated group showed much larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group, and the treatment difference (LIF 5.0% minus Placebo) in the mean change in VR_OSDI score at Day 84 was -0.28 (95% CI: -0.41, -0.14; p-value < 0.0001).

In the Phase 2 study, a dose response in the mean change in VR_OSDI was seen at Day 84 (See Figure 11). In this study, LIF 5.0% treated group showed numerically slightly larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in VR_OSDI score at Day 84 was -0.30 (95% CI: -0.63, 0.03; p-value = 0.0712).

In the OPUS-1 study, both treatment groups showed small and comparable mean reductions in VR_OSDI score from baseline throughout the study, and the treatment difference (LIF 5.0% minus Placebo) in the mean change in VR_OSDI score at Day 84 was -0.01 (95% CI: -0.12, 0.10) . Statistical significant difference was not achieved in this study (p-value = 0.8261).

Symptom Endpoint: Eye Dryness Score (EDS)

The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2 study and was supportive symptom endpoint in the Phase 2 and OPUS-1 studies; thus, confidence intervals and p-values reported in the Phase 2 and OPUS-1 studies were intended for descriptive use.

Statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated in OPUS-2 study. Both the Phase 2 and OPUS-1 studies showed numerically better improvement in the LIF 5.0% treated subjects over Placebo. Additionally, a dose response improvement of EDS was seen at Day 84 in the Phase 2 study.

In the OPUS-2 study, LIF 5.0% treated group showed much larger mean reduction in EDS from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in EDS at Day 84 was -12.3 (95% CI: -16.4, -8.3) and was strongly statistically significant (p-value < 0.0001).

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In OPUS-1 study, LIF 5.0% treated group showed slightly larger mean reduction in EDS from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in EDS at Day 84 was s -4.7 (95% CI: -8.9, -0.43; p-value = 0.0311). In this study, a much large improvement in EDS at Day 84 was observed in a small subgroup of subjects with a recent history of ATU and with baseline EDS ≥40. In this subgroup, the treatment difference in the mean change in EDS at Day 84 was -15.3 (95% CI: -25.9, -4.7). Note that the OPUS-2 study was designed based on the positive finding observed in this subgroup and used EDS as the primary symptom endpoint.

In the Phase 2 study, LIF 5.0% treated group showed slightly larger mean reduction in EDS from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in EDS at Day 84 was -7.6 (95% CI: -16.8, 1.5; p-value = 0.1021). Note that the likely reason the confidence interval for the treatment difference did not exclude zero was due to the smaller sample size compared to the OPUS-1 study.

5.3 Conclusion and Recommendation

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

Based on the totality of evidence, the statistical reviewer recommends for additional data from an adequate and well controlled study. The study, at a minimum, is expected to demonstrate statistical superiority of the test product over Placebo in improving a pre-defined clinical symptom. Furthermore, the test product in this study, at a minimum, is expected to show numerically better improvement in ICSS over Placebo or demonstrate similar level of reduction in ICSS seen in the OPUS-2 study.

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APPENDIX

Table 12: Mean Change in ICSS from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	1.65 (0.513)	1.77 (0.515)	1.81 (0.599)	1.84 (0.597)	2.40 (0.722)	2.39 (0.763)
Median	2.00	2.00	2.00	2.00	2.50	2.50
(95% CI)	(1.51, 1.78)	(1.63, 1.90)	(1.75, 1.88)	(1.78, 1.91)	(2.33, 2.47)	(2.31, 2.47)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	1.90 (0.760)	1.85 (0.596)	1.90 (0.705)	1.88 (0.704)	1.92 (0.910)	1.91 (0.966)
Median	2.00	2.00	2.00	2.00	2.00	2.00
(95% CI)	(1.69, 2.11)	(1.69, 2.01)	(1.82, 1.98)	(1.80, 1.96)	(1.82, 2.01)	(1.81, 2.01)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.85 (0.686)	1.87 (0.631)	1.79 (0.821)	1.71 (0.802)	1.79 (0.981)	1.70 (1.001)
Median	2.00	2.00	2.00	2.00	2.00	1.50
(95% CI)	(1.66, 2.03)	(1.70, 2.04)	(1.70, 1.89)	(1.61, 1.80)	(1.69, 1.90)	(1.60, 1.81)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	2.05 (0.715)	1.83 (0.680)	1.98 (0.874)	1.77 (0.879)	1.69 (1.010)	1.66 (1.044)
Median	2.00	2.00	2.00	2.00	1.50	1.50
(95% CI)	(1.85, 2.24)	(1.65, 2.02)	(1.88, 2.08)	(1.67, 1.87)	(1.59, 1.80)	(1.55, 1.77)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.25 (0.726)	0.06 (0.541)	0.08 (0.771)	0.04 (0.734)	-0.48 (0.800)	-0.48 (0.804)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
(95% CI)	(0.06, 0.45)	(-0.08, 0.21)	(-0.01, 0.17)	(-0.05, 0.12)	(-0.57, -0.40)	(-0.57, -0.40)
LS Means (SE)	0.23 (0.083)	0.09 (0.084)	0.08 (0.038)	0.05 (0.039)	-0.48 (0.041)	-0.49 (0.041)
Diff.(minus Placebo) (95% CI)		-0.13 (-0.37, 0.10)		-0.03 (-0.14, 0.08)		-0.00 (-0.12, 0.11)
P-value: ANCOVA		0.2591		0.5777		0.9518
P-value: Student T-test		0.1253		0.4783		0.9988
P-value: Wilcoxon Test		0.1575		0.4535		0.9602
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	0.20 (0.711)	0.08 (0.612)	-0.02 (0.893)	-0.14 (0.861)	-0.61 (0.899)	-0.69 (0.918)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
(95% CI)	(0.01, 0.39)	(-0.08, 0.25)	(-0.12, 0.08)	(-0.24, -0.04)	(-0.70, -0.51)	(-0.79, -0.59)
LS Means (SE)	0.16 (0.083)	0.12 (0.084)	-0.03 (0.046)	-0.13 (0.046)	-0.60 (0.046)	-0.69 (0.046)
Diff.(minus Placebo) (95% CI)		-0.04 (-0.28, 0.19)		-0.10 (-0.23, 0.02)		-0.09 (-0.21, 0.04)
P-value: ANCOVA		0.7097		0.1094		0.1756
P-value: Student T-test		0.3611		0.1044		0.2138
P-value: Wilcoxon Test		0.2857		0.0838		0.2642
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.40 (0.802)	0.05 (0.773)	0.17 (0.819)	-0.07 (0.868)	-0.71 (0.943)	-0.73 (0.926)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
(95% CI)	(0.18, 0.62)	(-0.16, 0.26)	(0.07, 0.26)	(-0.17, 0.03)	(-0.80, -0.61)	(-0.83, -0.64)
LS Means (SE)	0.35 (0.093)	0.10 (0.094)	0.16 (0.047)	-0.07 (0.047)	-0.70 (0.047)	-0.74 (0.047)
Diff.(minus Placebo) (95% CI)		-0.25 (-0.51, 0.02)		-0.23 (-0.36, -0.10)		-0.03 (-0.16, 0.10)
P-value: ANCOVA		0.0666		0.0007		0.6122
P-value: Student T-test		0.0209		0.0007		0.6768
P-value: Wilcoxon Test		0.0384		0.0006		0.7849

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Table 13: Mean Change in VR_OSDI from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	295	293	360	358
Mean (SD)	0.96 (0.865)	1.16 (1.148)	0.93 (0.958)	0.86 (0.931)	1.38 (1.065)	1.48 (1.062)
Median	1.00	0.75	0.67	0.50	1.25	1.42
(95% CI)	(0.74, 1.19)	(0.86, 1.46)	(0.82, 1.04)	(0.75, 0.96)	(1.27, 1.49)	(1.37, 1.59)
Day 14						
N	55	54	295	293	359	358
Mean (SD)	0.94 (0.983)	0.85 (1.057)	0.84 (0.862)	0.81 (0.895)	1.15 (0.999)	1.15 (1.049)
Median	0.67	0.50	0.67	0.50	1.00	1.00
(95% CI)	(0.68, 1.21)	(0.57, 1.14)	(0.74, 0.94)	(0.70, 0.91)	(1.05, 1.26)	(1.04, 1.26)
Day 42						
N	55	53	294	293	360	357
Mean (SD)	0.92 (0.924)	0.98 (1.041)	0.82 (0.878)	0.75 (0.850)	1.11 (1.044)	1.01 (1.053)
Median	0.50	0.75	0.50	0.50	1.00	0.67
(95% CI)	(0.67, 1.16)	(0.69, 1.27)	(0.72, 0.92)	(0.65, 0.85)	(1.00, 1.22)	(0.90, 1.12)
Day 84						
N	55	54	295	292	359	357
Mean (SD)	1.05 (1.173)	0.88 (0.961)	0.80 (0.838)	0.75 (0.861)	1.13 (1.047)	0.90 (0.998)
Median	0.67	0.67	0.50	0.50	1.00	0.50
(95% CI)	(0.74, 1.37)	(0.62, 1.14)	(0.71, 0.90)	(0.65, 0.85)	(1.03, 1.24)	(0.80, 1.01)
Change from Baseline to Day 14						
N	55	54	295	293	359	358
Mean (SD)	-0.04 (0.696)	-0.33 (0.910)	-0.09 (0.754)	-0.05 (0.744)	-0.23 (0.936)	-0.33 (0.986)
Median	0.00	0.00	0.00	0.00	0.00	-0.25
(95% CI)	(-0.23, 0.15)	(-0.58, -0.08)	(-0.18, -0.00)	(-0.14, 0.03)	(-0.32, -0.13)	(-0.44, -0.23)
LS Means (SE)	-0.07 (0.100)	-0.30 (0.101)	-0.08 (0.038)	-0.06 (0.038)	-0.25 (0.044)	-0.31 (0.044)
Diff.(minus Placebo) (95% CI)		-0.22 (-0.51, 0.06)		0.01 (-0.09, 0.12)		-0.06 (-0.18, 0.06)
P-value: ANCOVA		0.1236		0.8227		0.3250
P-value: Student T-test		0.0690		0.5380		0.1300
P-value: Wilcoxon Test		0.0462		0.6999		0.0272
Change from Baseline to Day 42						
N	55	53	294	293	360	357
Mean (SD)	-0.07 (0.738)	-0.22 (0.918)	-0.11 (0.777)	-0.11 (0.789)	-0.27 (1.016)	-0.48 (1.015)
Median	0.00	0.00	0.00	0.00	0.00	-0.33
(95% CI)	(-0.27, 0.13)	(-0.48, 0.03)	(-0.20, -0.02)	(-0.20, -0.02)	(-0.37, -0.16)	(-0.59, -0.38)
LS Means (SE)	-0.11 (0.100)	-0.18 (0.102)	-0.09 (0.039)	-0.12 (0.039)	-0.29 (0.047)	-0.46 (0.047)
Diff.(minus Placebo) (95% CI)		-0.07 (-0.36, 0.21)		-0.03 (-0.14, 0.08)		-0.16 (-0.29, -0.03)
P-value: ANCOVA		0.6089		0.5921		0.0149
P-value: Student T-test		0.3346		0.9976		0.0049
P-value: Wilcoxon Test		0.2761		0.7808		0.0017
Change from Baseline to Day 84						
N	55	54	295	292	359	357
Mean (SD)	0.07 (0.929)	-0.30 (0.934)	-0.12 (0.762)	-0.11 (0.829)	-0.25 (1.069)	-0.58 (1.100)
Median	0.00	0.00	0.00	0.00	0.00	-0.50
(95% CI)	(-0.18, 0.32)	(-0.56, -0.05)	(-0.21, -0.04)	(-0.20, -0.01)	(-0.36, -0.14)	(-0.70, -0.47)
LS Means (SE)	0 03 (0 116)	0 27 (0 117)	0 11 (0 039)	0 12 (0 039)	0 28 (0 048)	0 55 (0 048)
Diff.(minus Placebo) (95% CI)		-0.30 (-0.63, 0.03)		-0.01 (-0.12, 0.10)		-0.28 (-0.41, -0.14)
P-value: ANCOVA		0.0712		0.8261		<0.0001
P-value: Student T-test		0.0394		0.7860		<0.0001
P-value: Wilcoxon Test		0.0393		0.9063		<0.0001

Reference ID: 3938302

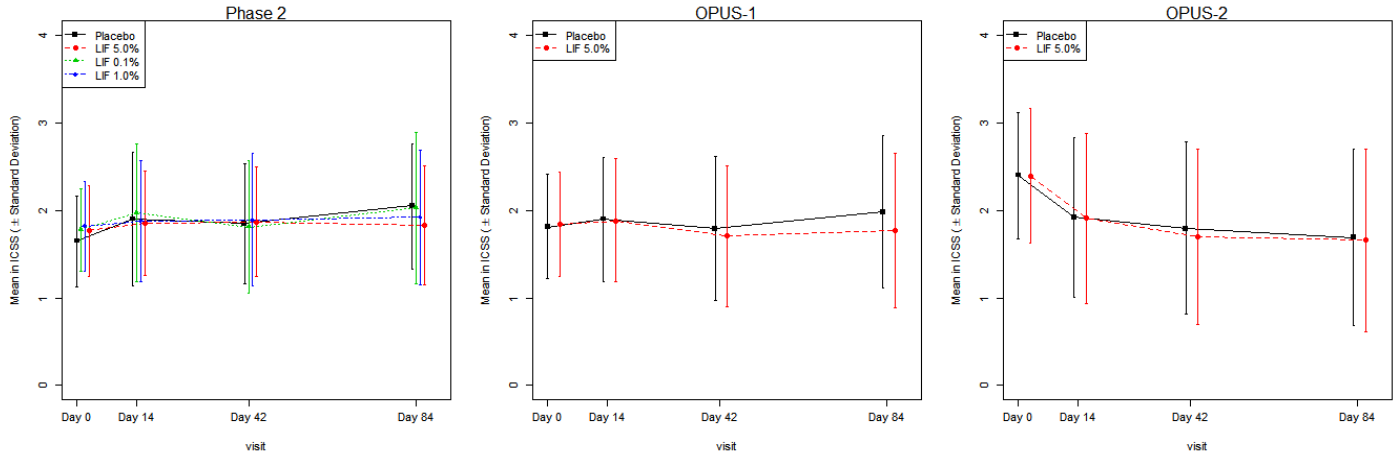
Table 14: Mean Change in EDS from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	57	295	293	360	358
Mean (SD)	51.81 (23.552)	51.58 (24.688)	41.62 (29.690)	40.18 (28.645)	69.22 (16.761)	69.68 (16.954)
Median	55.00	51.00	39.00	42.00	69.00	69.00
(95% CI)	(45.62, 58.00)	(45.03, 58.13)	(38.22, 45.02)	(36.88, 43.47)	(67.48, 70.95)	(67.92, 71.44)
Day 14						
N	54	54	295	293	360	358
Mean (SD)	47.48 (26.258)	42.37 (25.658)	34.13 (29.540)	33.44 (29.116)	56.24 (26.096)	50.20 (26.455)
Median	45.50	42.50	26.00	25.00	60.00	51.00
(95% CI)	(40.31, 54.65)	(35.37, 49.37)	(30.75, 37.52)	(30.10, 36.79)	(53.54, 58.95)	(47.45, 52.95)
Day 42						
N	55	54	295	293	360	358
Mean (SD)	43.27 (24.076)	33.61 (24.911)	32.48 (30.421)	27.56 (28.664)	51.23 (28.121)	41.31 (28.266)
Median	45.00	28.00	24.00	15.00	51.50	40.50
(95% CI)	(36.76, 49.78)	(26.81, 40.41)	(29.00, 35.97)	(24.27, 30.86)	(48.32, 54.15)	(38.37, 44.25)
Day 84						
N	55	54	295	293	360	358
Mean (SD)	44.11 (27.130)	37.06 (27.578)	30.39 (30.773)	25.00 (28.870)	46.47 (29.875)	34.39 (27.862)
Median	47.00	35.00	19.00	11.00	50.00	28.00
(95% CI)	(36.77, 51.44)	(29.53, 44.58)	(26.86, 33.91)	(21.68, 28.32)	(43.37, 49.56)	(31.49, 37.28)
Change from Baseline to Day 14						
N	54	53	295	293	360	358
Mean (SD)	-4.20 (26.384)	-9.58 (22.396)	-7.49 (29.007)	-6.73 (27.358)	-12.98 (24.102)	-19.48 (26.360)
Median	-2.50	-5.00	-4.00	-4.00	-8.00	-18.00
(95% CI)	(-11.41, 3.00)	(-15.76, -3.41)	(-10.81, -4.16)	(-9.88, -3.59)	(-15.47, -10.48)	(-22.22, -16.74)
LS Means (SE)	-4.36 (3.040)	-9.43 (3.068)	-7.15 (1.446)	-7.07 (1.450)	-13.1 (1.282)	-19.4 (1.285)
Diff.(minus Placebo) (95% CI)		-5.07 (-13.6, 3.49)		0.08 (-3.94, 4.11)		-6.33 (-9.90, -2.77)
P-value: ANCOVA		0.2429		0.9676		0.0005
P-value: Student T-test		0.2584		0.7458		0.0006
P-value: Wilcoxon Test		0.1970		0.8939		0.0002
Change from Baseline to Day 42						
N	55	53	295	293	360	358
Mean (SD)	-8.38 (20.046)	-18.58 (25.426)	-9.14 (30.033)	-12.61 (30.714)	-17.99 (26.603)	-28.37 (27.771)
Median	-5.00	-14.00	-4.00	-9.00	-14.00	-29.00
(95% CI)	(-13.80, -2.96)	(-25.59, -11.58)	(-12.58, -5.70)	(-16.15, -9.08)	(-20.74, -15.23)	(-31.26, -25.48)
LS Means (SE)	-8.54 (2.779)	-18.4 (2.831)	-8.76 (1.525)	-13.0 (1.530)	-18.1 (1.386)	-28.3 (1.389)
Diff.(minus Placebo) (95% CI)		-9.89 (-17.8, -2.02)		-4.24 (-8.48, 0.01)		-10.2 (-14.1, -6.36)
P-value: ANCOVA		0.0143		0.0503		0.0000
P-value: Student T-test		0.0222		0.1659		0.0000
P-value: Wilcoxon Test		0.0360		0.0669		<.0001
Change from Baseline to Day 84						
N	55	53	295	293	360	358
Mean (SD)	-7.55 (25.929)	-15.49 (25.987)	-11.23 (28.783)	-15.17 (31.482)	-22.75 (28.600)	-35.30 (28.400)
Median	-9.00	-7.00	-6.00	-9.00	-20.00	-39.00
(95% CI)	(-14.55, -0.54)	(-22.65, -8.33)	(-14.53, -7.94)	(-18.79, -11.55)	(-25.71, -19.79)	(-38.25, -32.34)
LS Means (SE)	-7.70 (3.240)	-15.3 (3.301)	-10.9 (1.530)	-15.5 (1.536)	-22.9 (1.450)	-35.2 (1.454)
Diff.(minus Placebo) (95% CI)		-7.63 (-16.8, 1.54)		-4.68 (-8.94, -0.43)		-12.3 (-16.4, -8.30)
P-value: ANCOVA		0.1021		0.0311		0.0000
P-value: Student T-test		0.1148		0.1137		0.0000
P-value: Wilcoxon Test		0.2890		0.1376		<.0001

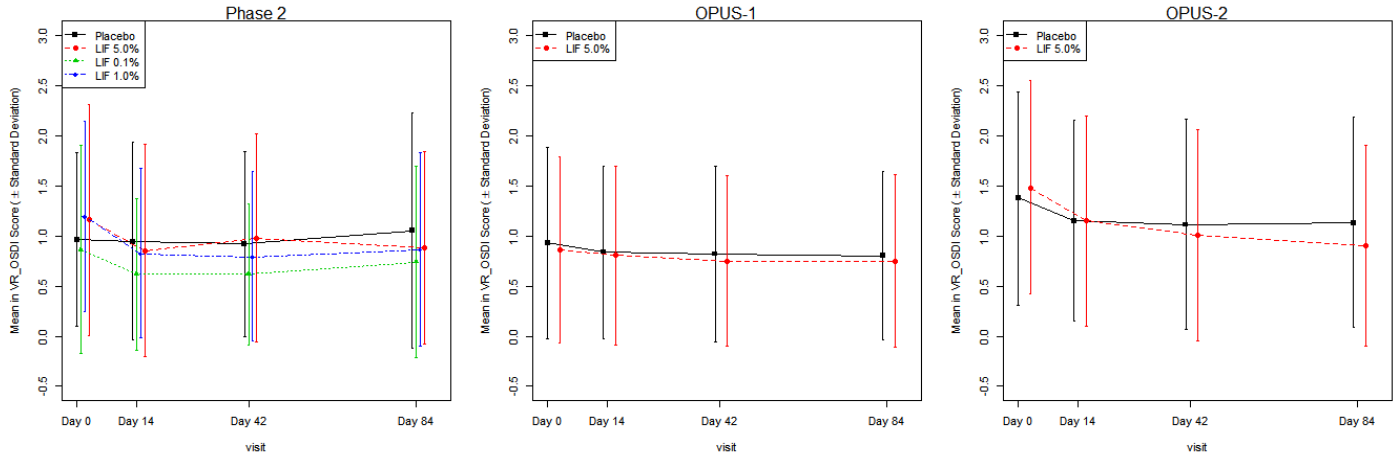
Reference ID: 3938302

Figure 32: Plot of the Actual Mean (± SD) in ICSS, VR_OSDI, and EDS for each Study
(ITT Population, LOCF)

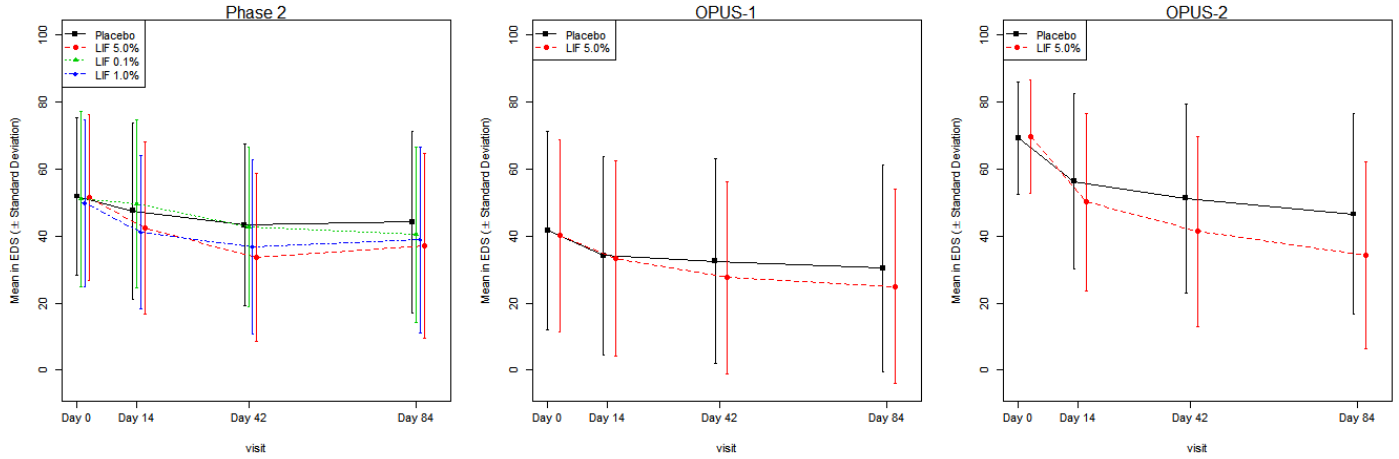
Inferior Corneal Staining Score (ICSS)



Visual-related function subscale of the Ocular Surface Disease Index (VR_OSDI)



Eye Dryness Score (EDS)



Reference ID: 3938302

Table 15: Mean Change in STT from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	4.67 (2.837)	5.02 (2.976)	4.69 (2.855)	4.90 (3.008)	5.12 (2.770)	5.46 (2.827)
Median	4.00	5.00	4.00	4.00	5.00	5.00
(95% CI)	(3.93, 5.42)	(4.23, 5.80)	(4.36, 5.02)	(4.56, 5.25)	(4.84, 5.41)	(5.17, 5.76)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	5.00 (3.621)	6.48 (3.785)	5.66 (5.074)	5.90 (4.815)	6.71 (5.192)	7.23 (5.803)
Median	4.00	7.00	4.00	5.00	5.00	6.00
(95% CI)	(4.02, 5.98)	(5.45, 7.51)	(5.08, 6.24)	(5.35, 6.45)	(6.17, 7.25)	(6.63, 7.84)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	5.76 (5.015)	6.70 (4.777)	6.19 (5.393)	6.63 (5.557)	7.43 (5.832)	7.97 (6.044)
Median	5.00	5.50	5.00	5.00	6.00	6.00
(95% CI)	(4.41, 7.12)	(5.40, 8.01)	(5.57, 6.81)	(5.99, 7.27)	(6.83, 8.04)	(7.34, 8.60)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	5.29 (4.383)	7.00 (5.924)	6.26 (5.598)	6.63 (5.772)	7.41 (5.626)	8.03 (6.248)
Median	4.00	5.50	5.00	5.00	6.00	7.00
(95% CI)	(4.11, 6.48)	(5.38, 8.62)	(5.62, 6.90)	(5.97, 7.30)	(6.82, 7.99)	(7.38, 8.68)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.27 (3.556)	1.50 (3.975)	0.97 (4.620)	1.00 (4.754)	1.59 (4.737)	1.77 (5.371)
Median	0.00	1.00	0.00	0.00	1.00	1.00
(95% CI)	(-0.69, 1.23)	(0.41, 2.59)	(0.44, 1.50)	(0.45, 1.54)	(1.10, 2.08)	(1.21, 2.33)
LS Means (SE)	0.21 (0.465)	1.57 (0.470)	0.93 (0.267)	1.03 (0.268)	1.55 (0.265)	1.81 (0.266)
Diff.(minus Placebo) (95% CI)		1.36 (0.05, 2.67)		0.10 (-0.64, 0.85)		0.26 (-0.48, 1.00)
P-value: ANCOVA		0.0419		0.7861		0.4942
P-value: Student T-test		0.0921		0.9440		0.6301
P-value: Wilcoxon Test		0.0577		0.9766		0.8516
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.04 (4.611)	1.72 (4.414)	1.50 (4.807)	1.73 (5.271)	2.31 (5.308)	2.51 (5.270)
Median	0.00	1.00	0.00	1.00	1.00	1.00
(95% CI)	(-0.21, 2.28)	(0.52, 2.93)	(0.94, 2.05)	(1.12, 2.33)	(1.76, 2.86)	(1.96, 3.06)
LS Means (SE)	1.00 (0.601)	1.76 (0.606)	1.47 (0.291)	1.75 (0.292)	2.31 (0.280)	2.51 (0.280)
Diff.(minus Placebo) (95% CI)		0.76 (-0.93, 2.45)		0.29 (-0.52, 1.10)		0.21 (-0.57, 0.98)
P-value: ANCOVA		0.3753		0.4882		0.6032
P-value: Student T-test		0.4295		0.5803		0.6174
P-value: Wilcoxon Test		0.2122		0.4987		0.5361
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.56 (4.525)	2.02 (6.218)	1.57 (5.072)	1.73 (5.445)	2.28 (5.211)	2.57 (5.606)
Median	0.00	1.00	1.00	1.00	1.00	1.00
(95% CI)	(-0.66, 1.79)	(0.32, 3.72)	(0.99, 2.15)	(1.10, 2.36)	(1.74, 2.82)	(1.98, 3.15)
LS Means (SE)	0.48 (0.690)	2.10 (0.697)	1.55 (0.304)	1.75 (0.305)	2.27 (0.286)	2.58 (0.286)
Diff.(minus Placebo) (95% CI)		1.62 (-0.33, 3.56)		0.21 (-0.64, 1.05)		0.32 (-0.48, 1.11)
P-value: ANCOVA		0.1023		0.6309		0.4331
P-value: Student T-test		0.1648		0.7087		0.4827
P-value: Wilcoxon Test		0.2046		0.7138		0.6142

Reference ID: 3938302

Table 16: Mean Change in Total CSS from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	4.43 (1.201)	4.33 (1.062)	4.83 (1.378)	4.84 (1.400)	5.18 (2.014)	5.09 (2.077)
Median	4.25	4.00	4.50	4.50	4.50	4.50
(95% CI)	(4.12, 4.75)	(4.05, 4.61)	(4.67, 4.99)	(4.68, 5.00)	(4.97, 5.39)	(4.88, 5.31)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	4.74 (1.853)	4.33 (1.292)	4.64 (1.764)	4.57 (1.738)	4.05 (2.293)	4.10 (2.339)
Median	5.00	4.00	4.50	4.50	3.50	3.50
(95% CI)	(4.24, 5.24)	(3.98, 4.69)	(4.44, 4.85)	(4.37, 4.77)	(3.82, 4.29)	(3.86, 4.34)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	4.52 (1.481)	4.44 (1.473)	4.34 (1.947)	4.04 (1.947)	3.90 (2.452)	3.63 (2.399)
Median	4.50	4.00	4.00	4.00	3.50	3.00
(95% CI)	(4.12, 4.92)	(4.03, 4.84)	(4.11, 4.56)	(3.82, 4.27)	(3.65, 4.16)	(3.38, 3.88)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	4.80 (1.862)	4.29 (1.439)	4.69 (2.146)	4.30 (2.180)	3.69 (2.459)	3.47 (2.548)
Median	4.50	4.00	4.50	4.00	3.50	3.00
(95% CI)	(4.30, 5.30)	(3.89, 4.68)	(4.45, 4.94)	(4.04, 4.55)	(3.43, 3.94)	(3.21, 3.74)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.29 (1.718)	0.00 (1.124)	-0.19 (1.772)	-0.27 (1.649)	-1.12 (1.773)	-0.99 (1.934)
Median	0.50	0.00	0.00	-0.50	-1.00	-1.00
(95% CI)	(-0.17, 0.76)	(-0.31, 0.31)	(-0.39, 0.01)	(-0.46, -0.09)	(-1.31, -0.94)	(-1.19, -0.79)
LS Means (SE)	0.31 (0.190)	-0.02 (0.192)	-0.19 (0.093)	-0.27 (0.093)	-1.11 (0.094)	-1.00 (0.094)
Diff.(minus Placebo) (95% CI)		-0.33 (-0.86, 0.21)		-0.08 (-0.34, 0.18)		0.11 (-0.15, 0.37)
P-value: ANCOVA		0.2274		0.5317		0.4236
P-value: Student T-test		0.2988		0.5431		0.3510
P-value: Wilcoxon Test		0.1851		0.2653		0.5026
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	0.07 (1.379)	0.10 (1.382)	-0.49 (1.931)	-0.80 (1.909)	-1.28 (2.017)	-1.46 (2.054)
Median	0.00	0.00	-0.50	-0.50	-1.50	-1.50
(95% CI)	(-0.30, 0.45)	(-0.28, 0.48)	(-0.71, -0.27)	(-1.02, -0.58)	(-1.48, -1.07)	(-1.68, -1.25)
LS Means (SE)	0.09 (0.177)	0.08 (0.178)	-0.50 (0.104)	-0.80 (0.104)	-1.26 (0.103)	-1.47 (0.103)
Diff.(minus Placebo) (95% CI)		-0.02 (-0.51, 0.48)		-0.30 (-0.59, -0.01)		-0.21 (-0.50, 0.07)
P-value: ANCOVA		0.9516		0.0411		0.1478
P-value: Student T-test		0.9125		0.0544		0.2181
P-value: Wilcoxon Test		0.9683		0.0329		0.1109
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.35 (1.638)	-0.05 (1.461)	-0.14 (1.923)	-0.55 (1.989)	-1.49 (2.097)	-1.62 (2.043)
Median	0.00	0.00	0.00	-0.50	-1.50	-1.75
(95% CI)	(-0.09, 0.80)	(-0.45, 0.35)	(-0.36, 0.08)	(-0.77, -0.32)	(-1.71, -1.27)	(-1.83, -1.41)
LS Means (SE)	0.37 (0.203)	-0.07 (0.205)	-0.14 (0.112)	-0.55 (0.112)	-1.48 (0.105)	-1.63 (0.106)
Diff.(minus Placebo) (95% CI)		-0.44 (-1.01, 0.13)		-0.41 (-0.72, -0.10)		-0.16 (-0.45, 0.14)
P-value: ANCOVA		0.1285		0.0106		0.2973
P-value: Student T-test		0.1806		0.0117		0.3910
P-value: Wilcoxon Test		0.2538		0.0021		0.2438

Reference ID: 3938302

Table 17: Mean Change in Nasal CLGSS from baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	1.80 (0.932)	1.69 (0.766)	1.90 (0.843)	2.03 (0.814)	2.14 (1.045)	2.13 (1.039)
Median	2.00	2.00	2.00	2.00	2.50	2.00
(95% CI)	(1.56, 2.05)	(1.49, 1.89)	(1.80, 1.99)	(1.94, 2.12)	(2.03, 2.25)	(2.02, 2.23)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	1.83 (1.033)	1.81 (0.803)	1.94 (0.866)	1.89 (0.815)	1.92 (1.045)	1.97 (1.072)
Median	2.00	2.00	2.00	2.00	2.00	2.00
(95% CI)	(1.55, 2.11)	(1.59, 2.02)	(1.84, 2.04)	(1.80, 1.99)	(1.81, 2.02)	(1.86, 2.08)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.67 (0.949)	1.77 (0.856)	1.89 (0.850)	1.84 (0.838)	1.89 (1.080)	1.83 (1.065)
Median	2.00	2.00	2.00	2.00	2.00	2.00
(95% CI)	(1.42, 1.93)	(1.53, 2.00)	(1.80, 1.99)	(1.74, 1.94)	(1.78, 2.00)	(1.72, 1.94)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	1.83 (1.051)	1.83 (0.890)	1.85 (0.919)	1.80 (0.830)	1.86 (1.090)	1.88 (1.091)
Median	2.00	2.00	2.00	2.00	2.00	1.75
(95% CI)	(1.54, 2.11)	(1.59, 2.08)	(1.74, 1.95)	(1.70, 1.89)	(1.75, 1.98)	(1.76, 1.99)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.05 (0.743)	0.14 (0.655)	0.04 (0.671)	-0.14 (0.710)	-0.22 (0.743)	-0.16 (0.861)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.15, 0.26)	(-0.04, 0.32)	(-0.04, 0.12)	(-0.22, -0.05)	(-0.30, -0.15)	(-0.25, -0.07)
LS Means (SE)	0.07 (0.091)	0.13 (0.092)	0.02 (0.037)	-0.11 (0.037)	-0.22 (0.039)	-0.16 (0.039)
Diff.(minus Placebo) (95% CI)		0.06 (-0.20, 0.31)		-0.13 (-0.24, -0.03)		0.06 (-0.05, 0.17)
P-value: ANCOVA		0.6520		0.0114		0.2835
P-value: Student T-test		0.5312		0.0020		0.2837
P-value: Wilcoxon Test		0.2745		0.0036		0.4304
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	-0.10 (0.655)	0.10 (0.716)	-0.00 (0.749)	-0.19 (0.757)	-0.25 (0.766)	-0.29 (0.933)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.28, 0.08)	(-0.09, 0.30)	(-0.09, 0.08)	(-0.27, -0.10)	(-0.33, -0.17)	(-0.39, -0.20)
LS Means (SE)	-0.09 (0.088)	0.09 (0.089)	-0.03 (0.040)	-0.16 (0.040)	-0.25 (0.042)	-0.30 (0.042)
Diff.(minus Placebo) (95% CI)		0.17 (-0.07, 0.42)		-0.14 (-0.25, -0.02)		-0.05 (-0.16, 0.07)
P-value: ANCOVA		0.1672		0.0164		0.4087
P-value: Student T-test		0.1276		0.0029		0.4831
P-value: Wilcoxon Test		0.2106		0.0019		0.2679
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.05 (0.711)	0.17 (0.818)	-0.05 (0.743)	-0.23 (0.776)	-0.27 (0.805)	-0.25 (0.850)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.14, 0.25)	(-0.06, 0.39)	(-0.14, 0.03)	(-0.32, -0.14)	(-0.36, -0.19)	(-0.34, -0.16)
LS Means (SE)	0.07 (0.100)	0.15 (0.101)	-0.07 (0.041)	-0.21 (0.041)	-0.27 (0.041)	-0.25 (0.041)
Diff.(minus Placebo) (95% CI)		0.09 (-0.20, 0.37)		-0.14 (-0.25, -0.02)		0.02 (-0.09, 0.14)
P-value: ANCOVA		0.5472		0.0195		0.7118
P-value: Student T-test		0.4467		0.0037		0.6858
P-value: Wilcoxon Test		0.3952		0.0055		0.7598

Reference ID: 3938302

Table 18: Mean Change in Total OSDI Score from baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	295	293	360	358
Mean (SD)	28.84 (16.499)	31.77 (21.312)	27.05 (18.147)	26.03 (19.042)	39.83 (20.435)	40.78 (21.845)
Median	29.58	27.29	22.73	20.83	39.58	37.50
(95% CI)	(24.50, 33.17)	(26.16, 37.37)	(24.97, 29.13)	(23.84, 28.22)	(37.71, 41.95)	(38.51, 43.05)
Day 14						
N	55	54	295	293	360	358
Mean (SD)	29.43 (18.937)	27.49 (19.441)	24.71 (17.625)	24.70 (17.781)	34.87 (20.298)	33.66 (21.587)
Median	22.92	21.16	20.45	20.45	31.82	29.17
(95% CI)	(24.31, 34.55)	(22.18, 32.79)	(22.69, 26.73)	(22.65, 26.74)	(32.77, 36.98)	(31.42, 35.91)
Day 42						
N	55	54	295	293	360	358
Mean (SD)	27.98 (18.033)	29.39 (19.676)	23.78 (17.844)	23.63 (17.860)	33.85 (21.090)	30.59 (22.676)
Median	25.00	25.00	19.44	20.00	31.25	25.00
(95% CI)	(23.10, 32.85)	(24.02, 34.76)	(21.74, 25.83)	(21.58, 25.69)	(31.66, 36.03)	(28.23, 32.94)
Day 84						
N	55	54	295	293	360	358
Mean (SD)	29.43 (20.906)	27.99 (20.732)	23.21 (17.239)	23.05 (18.268)	32.14 (22.192)	27.01 (21.763)
Median	25.00	22.36	20.00	18.75	28.47	22.50
(95% CI)	(23.77, 35.08)	(22.33, 33.65)	(21.24, 25.19)	(20.95, 25.15)	(29.84, 34.44)	(24.75, 29.28)
Change from Baseline to Day 14						
N	55	54	295	293	360	358
Mean (SD)	-0.09 (10.069)	-5.15 (14.149)	-2.34 (14.000)	-1.33 (13.405)	-4.96 (16.373)	-7.12 (19.358)
Median	0.00	-2.18	-2.08	-0.23	-4.17	-4.92
(95% CI)	(-2.81, 2.64)	(-9.01, -1.29)	(-3.94, -0.74)	(-2.87, 0.21)	(-6.66, -3.26)	(-9.13, -5.11)
LS Means (SE)	-0.40 (1.580)	-4.83 (1.595)	-2.18 (0.721)	-1.49 (0.724)	-5.13 (0.851)	-6.95 (0.853)
Diff.(minus Placebo) (95% CI)		-4.44 (-8.89, 0.02)		0.68 (-1.32, 2.69)		-1.82 (-4.18, 0.55)
P-value: ANCOVA		0.0512		0.5035		0.1319
P-value: Student T-test		0.0333		0.3731		0.1067
P-value: Wilcoxon Test		0.1698		0.1891		0.1314
Change from Baseline to Day 42						
N	55	54	295	293	360	358
Mean (SD)	-1.53 (9.776)	-3.25 (14.629)	-3.27 (14.164)	-2.40 (15.299)	-5.99 (17.799)	-10.20 (19.325)
Median	-2.27	-0.97	-2.27	-2.08	-5.89	-9.09
(95% CI)	(-4.18, 1.11)	(-7.24, 0.74)	(-4.89, -1.64)	(-4.16, -0.64)	(-7.83, -4.14)	(-12.21, -8.19)
LS Means (SE)	-1.88 (1.583)	-2.90 (1.597)	-3.09 (0.769)	-2.58 (0.772)	-6.16 (0.899)	-10.0 (0.901)
Diff.(minus Placebo) (95% CI)		-1.02 (-5.48, 3.45)		0.51 (-1.63, 2.65)		-3.86 (-6.36, -1.37)
P-value: ANCOVA		0.6529		0.6416		0.0025
P-value: Student T-test		0.4728		0.4752		0.0025
P-value: Wilcoxon Test		0.8748		0.5792		0.0012
Change from Baseline to Day 84						
N	55	54	295	293	360	358
Mean (SD)	-0.09 (13.633)	-4.65 (15.223)	-3.84 (14.949)	-2.98 (15.250)	-7.69 (20.247)	-13.77 (21.255)
Median	-1.14	-1.59	-2.50	-1.67	-6.25	-12.41
(95% CI)	(-3.77, 3.60)	(-8.80, -0.49)	(-5.55, -2.12)	(-4.73, -1.22)	(-9.79, -5.59)	(-15.98, -11.56)
LS Means (SE)	-0.38 (1.896)	-4.34 (1.914)	-3.65 (0.783)	-3.17 (0.786)	-7.91 (0.979)	-13.6 (0.981)
Diff.(minus Placebo) (95% CI)		-3.96 (-9.31, 1.39)		0.48 (-1.70, 2.65)		-5.64 (-8.36, -2.92)
P-value: ANCOVA		0.1451		0.6686		0.0001
P-value: Student T-test		0.1023		0.4904		0.0001
P-value: Wilcoxon Test		0.1905		0.5056		<.0001

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Table 19: Mean Change in ODS Score from baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	2.03 (1.169)	2.03 (1.042)	1.78 (1.161)	1.66 (1.191)	2.29 (1.080)	2.30 (1.030)
Median	2.00	2.00	2.00	2.00	3.00	2.00
(95% CI)	(1.73, 2.34)	(1.76, 2.31)	(1.65, 1.91)	(1.52, 1.79)	(2.18, 2.40)	(2.19, 2.41)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	1.82 (1.234)	1.76 (1.164)	1.49 (1.159)	1.47 (1.127)	1.99 (1.175)	1.95 (1.160)
Median	2.00	1.00	1.00	1.00	2.00	2.00
(95% CI)	(1.48, 2.15)	(1.44, 2.08)	(1.36, 1.63)	(1.34, 1.60)	(1.87, 2.11)	(1.83, 2.07)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.71 (1.083)	1.41 (1.073)	1.35 (1.178)	1.27 (1.187)	1.89 (1.188)	1.66 (1.200)
Median	2.00	1.00	1.00	1.00	2.00	2.00
(95% CI)	(1.42, 2.00)	(1.11, 1.70)	(1.21, 1.48)	(1.13, 1.41)	(1.77, 2.01)	(1.53, 1.78)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	1.67 (1.037)	1.46 (1.177)	1.31 (1.182)	1.10 (1.153)	1.72 (1.233)	1.39 (1.124)
Median	2.00	1.50	1.00	1.00	2.00	1.00
(95% CI)	(1.39, 1.95)	(1.14, 1.78)	(1.18, 1.45)	(0.97, 1.23)	(1.59, 1.85)	(1.27, 1.51)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	-0.22 (1.066)	-0.30 (1.283)	-0.29 (1.337)	-0.19 (1.283)	-0.30 (1.215)	-0.35 (1.239)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.51, 0.07)	(-0.65, 0.05)	(-0.44, -0.13)	(-0.34, -0.04)	(-0.43, -0.18)	(-0.48, -0.22)
LS Means (SE)	-0.22 (0.143)	-0.29 (0.144)	-0.25 (0.062)	-0.23 (0.062)	-0.30 (0.057)	-0.35 (0.057)
Diff.(minus Placebo) (95% CI)		-0.07 (-0.47, 0.33)		0.02 (-0.16, 0.19)		-0.05 (-0.20, 0.11)
P-value: ANCOVA		0.7345		0.8368		0.5676
P-value: Student T-test		0.7301		0.3654		0.5914
P-value: Wilcoxon Test		0.5350		0.4113		0.6046
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	-0.33 (1.037)	-0.65 (1.320)	-0.43 (1.343)	-0.39 (1.357)	-0.40 (1.245)	-0.64 (1.327)
Median	0.00	-1.00	0.00	0.00	0.00	-1.00
(95% CI)	(-0.61, -0.05)	(-1.01, -0.29)	(-0.59, -0.28)	(-0.54, -0.23)	(-0.53, -0.27)	(-0.78, -0.50)
LS Means (SE)	-0.33 (0.133)	-0.64 (0.134)	-0.39 (0.065)	-0.43 (0.065)	-0.40 (0.059)	-0.64 (0.059)
Diff.(minus Placebo) (95% CI)		-0.31 (-0.68, 0.07)		-0.03 (-0.21, 0.15)		-0.23 (-0.40, -0.07)
P-value: ANCOVA		0.1050		0.7152		0.0051
P-value: Student T-test		0.1607		0.6778		0.0128
P-value: Wilcoxon Test		0.1865		0.8559		0.0083
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	-0.36 (1.112)	-0.59 (1.421)	-0.47 (1.379)	-0.56 (1.368)	-0.57 (1.354)	-0.91 (1.280)
Median	0.00	-1.00	0.00	0.00	-1.00	-1.00
(95% CI)	(-0.66, -0.06)	(-0.98, -0.20)	(-0.62, -0.31)	(-0.71, -0.40)	(-0.71, -0.43)	(-1.04, -0.78)
LS Means (SE)	-0.37 (0.141)	-0.59 (0.143)	-0.42 (0.065)	-0.60 (0.065)	-0.57 (0.059)	-0.91 (0.059)
Diff.(minus Placebo) (95% CI)		-0.22 (-0.61, 0.18)		-0.18 (-0.36, 0.01)		-0.34 (-0.50, -0.17)
P-value: ANCOVA		0.2841		0.0572		0.0001
P-value: Student T-test		0.3504		0.4259		0.0006
P-value: Wilcoxon Test		0.4506		0.7462		0.0003

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Table 20: Mean Change in EDisS Score from Baseline by Visit
(ITT Population, LOCF)

	OPUS-2	
Summary	**Placebo**	**LIF 5.0%**
Baseline		
N	360	358
Mean (SD)	55.53 (24.927)	56.15 (25.386)
Median	56.50	56.00
(95% CI)	(52.95, 58.11)	(53.51, 58.79)
Day 14		
N	360	358
Mean (SD)	45.07 (26.842)	44.12 (28.039)
Median	48.00	48.00
(95% CI)	(42.29, 47.85)	(41.20, 47.03)
Day 42		
N	360	358
Mean (SD)	42.72 (28.737)	36.38 (28.407)
Median	46.00	34.50
(95% CI)	(39.74, 45.70)	(33.42, 39.33)
Day 84		
N	360	358
Mean (SD)	38.80 (30.191)	29.69 (26.432)
Median	39.00	24.00
(95% CI)	(35.67, 41.93)	(26.94, 32.44)
Change from Baseline to Day 14		
N	360	358
Mean (SD)	-10.46 (25.643)	-12.03 (30.105)
Median	-7.00	-8.00
(95% CI)	(-13.12, -7.80)	(-15.16, -8.90)
LS Means (SE)	-10.6 (1.297)	-11.9 (1.300)
Diff.(minus Placebo) (95% CI)		-1.25 (-4.85, 2.36)
P-value: ANCOVA		0.4978
P-value: Student T-test		0.4522
P-value: Wilcoxon Test		0.4481
Change from Baseline to Day 42		
N	360	358
Mean (SD)	-12.81 (29.167)	-19.77 (32.412)
Median	-8.50	-20.50
(95% CI)	(-15.84, -9.79)	(-23.14, -16.40)
LS Means (SE)	-13.0 (1.400)	-19.6 (1.404)
Diff.(minus Placebo) (95% CI)		-6.52 (-10.4, -2.63)
P-value: ANCOVA		0.0011
P-value: Student T-test		0.0026
P-value: Wilcoxon Test		0.0007
Change from Baseline to Day 84		
N	360	358
Mean (SD)	-16.73 (31.207)	-26.46 (31.238)
Median	-14.00	-26.00
(95% CI)	(-19.97, -13.50)	(-29.70, -23.21)
LS Means (SE)	-17.0 (1.413)	-26.2 (1.417)
Diff.(minus Placebo) (95% CI)		-9.28 (-13.2, -5.35)
P-value: ANCOVA		0.0000
P-value: Student T-test		0.0000
P-value: Wilcoxon Test		<.0001

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Table 21: Mean change (± SE) in EDS by History of ATU and Baseline EDS in OPUS-1
(ITT Population, LOCF)

	ATU & EDS ≥ 40		Other	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline				
N	67	63	228	230
Mean (SD)	67.82 (18.211)	63.97 (18.542)	33.92 (27.984)	33.66 (27.474)
Median	61.00	58.00	26.00	27.00
(95% CI)	(63.38, 72.26)	(59.30, 68.64)	(30.27, 37.57)	(30.09, 37.23)
Day 14				
N	67	63	228	230
Mean (SD)	45.82 (30.343)	43.57 (28.692)	30.70 (28.466)	30.67 (28.672)
Median	50.00	44.00	22.50	21.00
(95% CI)	(38.42, 53.22)	(36.35, 50.80)	(26.98, 34.41)	(26.94, 34.39)
Day 42				
N	67	63	228	230
Mean (SD)	48.51 (32.859)	32.71 (28.287)	27.77 (28.046)	26.15 (28.666)
Median	51.00	27.00	18.00	12.00
(95% CI)	(40.49, 56.52)	(25.59, 39.84)	(24.11, 31.43)	(22.43, 29.88)
Day 84				
N	67	63	228	230
Mean (SD)	45.76 (33.315)	28.57 (28.072)	25.87 (28.522)	24.03 (29.068)
Median	42.00	21.00	15.00	9.00
(95% CI)	(37.63, 53.89)	(21.50, 35.64)	(22.15, 29.59)	(20.25, 27.80)
Change from Baseline to Day 14				
N	67	63	228	230
Mean (SD)	-22.00 (34.366)	-20.40 (29.463)	-3.22 (25.807)	-2.99 (25.571)
Median	-18.00	-19.00	-2.00	-1.00
(95% CI)	(-30.38, -13.62)	(-27.82, -12.98)	(-6.59, 0.14)	(-6.31, 0.33)
LS Means (SE)	-20.7 (3.619)	-21.8 (3.733)	-3.16 (1.528)	-3.06 (1.521)
Diff.(minus Placebo) (95% CI)		-1.05 (-11.4, 9.29)		0.10 (-4.14, 4.34)
P-value: ANCOVA		0.8412		0.9626
P-value: Student T-test		0.7763		0.9229
P-value: Wilcoxon Test		0.9443		0.8091
Change from Baseline to Day 42				
N	67	63	228	230
Mean (SD)	-19.31 (32.516)	-31.25 (29.648)	-6.15 (28.657)	-7.51 (29.036)
Median	-12.00	-31.00	-3.00	-5.00
(95% CI)	(-27.24, -11.38)	(-38.72, -23.79)	(-9.89, -2.41)	(-11.28, -3.74)
LS Means (SE)	-18.3 (3.670)	-32.3 (3.786)	-6.06 (1.647)	-7.60 (1.640)
Diff.(minus Placebo) (95% CI)		-14.1 (-24.5, -3.57)		-1.54 (-6.11, 3.03)
P-value: ANCOVA		0.0090		0.5083
P-value: Student T-test		0.0308		0.6143
P-value: Wilcoxon Test		0.0166		0.4144
Change from Baseline to Day 84				
N	67	63	228	230
Mean (SD)	-22.06 (31.591)	-35.40 (31.722)	-8.05 (27.168)	-9.63 (29.121)
Median	-24.00	-38.00	-4.00	-5.00
(95% CI)	(-29.77, -14.35)	(-43.39, -27.41)	(-11.60, -4.51)	(-13.42, -5.85)
LS Means (SE)	-21.1 (3.699)	-36.4 (3.816)	-7.98 (1.650)	-9.71 (1.643)
Diff.(minus Placebo) (95% CI)		-15.3 (-25.9, -4.71)		-1.73 (-6.31, 2.85)
P-value: ANCOVA		0.0050		0.4581
P-value: Student T-test		0.0178		0.5481
P-value: Wilcoxon Test		0.0269		0.5078

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Table 22: Sensitivity Analysis for the Mean Change in Signs and Symptoms from Baseline at Day 84 (Observed Cases)
(ITT Population)

Phase 2

	Parameters	LSM (SE)		Difference in LSM (95% CI)	P-value
		Placebo (N = 47)	LIF 5.0% (N = 48)		
Sign	ICSS	0.30 (0.101)	0.06 (0.100)	-0.24 (-0.52, 0.05)	0.1006
	Nasal CLGSS	0.05 (0.106)	0.20 (0.105)	0.15 (-0.15, 0.44)	0.3325
	STT	0.36 (0.796)	2.05 (0.779)	1.69 (-0.53, 3.90)	0.1333
	Total CSS	0.45 (0.221)	-0.06 (0.219)	-0.51 (-1.13, 0.11)	0.1071
Symptom	EDS	-7.53 (3.504)	-15.2 (3.504)	-7.64 (-17.5, 2.20)	0.1266
	TOTAL OSDI	-0.67 (2.100)	-5.18 (2.100)	-4.50 (-10.4, 1.41)	0.1336
	VR_OSDI	0.05 (0.125)	-0.33 (0.125)	-0.37 (-0.73, -0.02)	0.0367
	ODS	-0.33 (0.152)	-0.63 (0.150)	-0.30 (-0.73, 0.12)	0.1608

OPUS-1

	Parameters	Placebo (N = 283)	LIF 5.0% (N = 281)	Difference in LSM (95% CI)	P-value
Sign	ICSS	0.17 (0.048)	-0.08 (0.048)	-0.25 (-0.39, -0.12)	0.0003
	Nasal CLGSS	-0.08 (0.042)	-0.21 (0.042)	-0.13 (-0.25, -0.02)	0.0249
	STT	1.50 (0.312)	1.84 (0.313)	0.34 (-0.53, 1.21)	0.4437
	Total CSS	-0.11 (0.115)	-0.56 (0.116)	-0.45 (-0.77, -0.13)	0.0057
Symptom	EDS	-10.8 (1.575)	-15.8 (1.581)	-4.98 (-9.37, -0.59)	0.0261
	TOTAL OSDI	-3.49 (0.801)	-3.31 (0.805)	0.17 (-2.06, 2.41)	0.8783
	VR_OSDI	-0.10 (0.040)	-0.13 (0.040)	-0.02 (-0.14, 0.09)	0.664
	ODS	-0.42 (0.066)	-0.62 (0.067)	-0.20 (-0.39, -0.02)	0.0317

OPUS-2

	Parameters	Placebo (N = 350)	LIF 5.0% (N = 328)	Difference in LSM (95% CI)	P-value
Sign	ICSS	-0.71 (0.048)	-0.76 (0.049)	-0.05 (-0.18, 0.09)	0.4749
	Nasal CLGSS	-0.28 (0.041)	-0.26 (0.042)	0.02 (-0.09, 0.14)	0.7149
	STT	2.23 (0.289)	2.65 (0.299)	0.42 (-0.40, 1.23)	0.3172
	Total CSS	-1.50 (0.107)	-1.70 (0.110)	-0.20 (-0.50, 0.10)	0.2012
Symptom	EDS	-23.3 (1.444)	-36.9 (1.491)	-13.6 (-17.7, -9.55)	<.0001
	TOTAL OSDI	-8.22 (0.942)	-15.0 (0.973)	-6.77 (-9.43, -4.11)	<.0001
	VR_OSDI	-0.29 (0.046)	-0.62 (0.048)	-0.33 (-0.46, -0.20)	<.0001
	ODS	-0.59 (0.058)	-0.97 (0.060)	-0.39 (-0.55, -0.22)	<.0001
	EDisS	-17.6 (1.393)	-28.2 (1.439)	-10.6 (-14.5, -6.66)	<.0001

ICSS: Inferior corneal staining score; Total CSS: Total corneal staining score; Nasal CLGSS: Nasal conjunctival lissamine green staining score; STT: Schirmer Tear Test (mm/5 minutes); EDS: Eye Dryness Score (VAS); OSDI: Ocular Surface Disease Index; VR_OSDI: Vision related OSDI; EDisS: Eye Discomfort Score (VAS); ODS: Ocular Discomfort Score.

LSM: Least Square Mean; SE: Standard Error.

Reference ID: 3938302

Table 23: Sensitivity Analysis for the Mean Change in Signs and Symptoms from Baseline at Day 84 (WOCF)
(ITT Population)

Phase 2

	Parameters	LSM (SE)		Difference in LSM (95% CI)	P-value
		Placebo (N = 58)	LIF 5.0% (N = 58)		
Sign	ICSS	0.34 (0.089)	0.11 (0.089)	-0.23 (-0.48, 0.02)	0.0732
	Nasal CLGSS	0.09 (0.091)	0.19 (0.091)	0.10 (-0.16, 0.35)	0.4489
	STT	0.11 (0.651)	1.66 (0.651)	1.55 (-0.28, 3.37)	0.0961
	Total CSS	0.41 (0.185)	0.05 (0.185)	-0.35 (-0.87, 0.17)	0.1806
Symptom	EDS	-4.55 (3.061)	-12.4 (3.087)	-7.81 (-16.4, 0.80)	0.0750
	TOTAL OSDI	0.29 (1.795)	-3.62 (1.795)	-3.91 (-8.95, 1.12)	0.1265
	VR_OSDI	0.06 (0.108)	-0.21 (0.108)	-0.28 (-0.58, 0.03)	0.0731
	ODS	-0.21 (0.136)	-0.50 (0.136)	-0.29 (-0.68, 0.09)	0.1317

OPUS-1

	Parameters	Placebo (N = 294)	LIF 5.0% (N = 293)	Difference in LSM (95% CI)	P-value
Sign	ICSS	0.18 (0.047)	-0.06 (0.047)	-0.25 (-0.38, -0.11)	0.0002
	Nasal CLGSS	-0.07 (0.041)	-0.20 (0.041)	-0.13 (-0.25, -0.02)	0.0198
	STT	1.41 (0.302)	1.73 (0.302)	0.33 (-0.51, 1.16)	0.4467
	Total CSS	-0.09 (0.111)	-0.51 (0.111)	-0.43 (-0.74, -0.12)	0.0066
Symptom	EDS	-10.7 (1.530)	-15.0 (1.530)	-4.30 (-8.55, -0.05)	0.0476
	TOTAL OSDI	-3.19 (0.781)	-3.10 (0.782)	0.08 (-2.09, 2.25)	0.9392
	VR_OSDI	-0.09 (0.039)	-0.12 (0.039)	-0.03 (-0.14, 0.08)	0.6349
	ODS	-0.40 (0.065)	-0.58 (0.065)	-0.18 (-0.36, -0.00)	0.0492

OPUS-2

	Parameters	Placebo (N = 360)	LIF 5.0% (N = 358)	Difference in LSM (95% CI)	P-value
Sign	ICSS	-0.68 (0.047)	-0.68 (0.048)	0.01 (-0.13, 0.14)	0.9335
	Nasal CLGSS	-0.26 (0.041)	-0.21 (0.041)	0.05 (-0.06, 0.17)	0.3634
	STT	2.16 (0.282)	2.31 (0.282)	0.15 (-0.63, 0.94)	0.7025
	Total CSS	-1.44 (0.106)	-1.52 (0.106)	-0.08 (-0.37, 0.22)	0.6041
Symptom	EDS	-22.2 (1.476)	-33.3 (1.480)	-11.1 (-15.2, -7.01)	<.0001
	TOTAL OSDI	-7.75 (0.987)	-12.7 (0.990)	-4.98 (-7.72, -2.23)	0.0004
	VR_OSDI	-0.27 (0.048)	-0.52 (0.049)	-0.25 (-0.39, -0.12)	0.0002
	ODS	-0.55 (0.059)	-0.86 (0.060)	-0.31 (-0.47, -0.14)	0.0003
	EDisS	-16.6 (1.438)	-24.8 (1.442)	-8.25 (-12.3, -4.26)	<.0001

WOCF: Worst observation carried forward.

;

Reference ID: 3938302

Table 24: Sensitivity Analysis for the Mean Change in Signs and Symptoms from Baseline at Day 84 (MRMM Analysis)
(ITT Population)

Phase 2

	Parameters	LSM (SE)		Difference in LSM (95% CI)	P-value
		Placebo (N = 47)	LIF 5.0% (N = 48)		
Sign	ICSS	0.35 (0.106)	0.09 (0.101)	-0.26 (-0.54, 0.02)	0.0721
	Nasal CLGSS	0.01 (0.098)	0.12 (0.114)	0.12 (-0.17, 0.40)	0.4206
	STT	0.30 (0.652)	2.00 (0.898)	1.70 (-0.46, 3.85)	0.1209
	Total CSS	0.40 (0.242)	-0.09 (0.201)	-0.49 (-1.10, 0.11)	0.1105
Symptom	EDS	-7.34 (3.504)	-14.5 (3.654)	-7.15 (-16.8, 2.48)	0.1438
	TOTAL OSDI	0.06 (2.122)	-3.90 (2.151)	-3.96 (-9.75, 1.83)	0.1781
	VR_OSDI	0.07 (0.140)	-0.27 (0.113)	-0.34 (-0.68, 0.00)	0.0530
	ODS	-0.31 (0.134)	-0.58 (0.181)	-0.27 (-0.70, 0.16)	0.2138

OPUS-1

	Parameters	Placebo (N = 283)	LIF 5.0% (N = 281)	Difference in LSM (95% CI)	P-value
Sign	ICSS	0.12 (0.051)	-0.13 (0.054)	-0.24 (-0.38, -0.11)	0.0003
	Nasal CLGSS	-0.14 (0.047)	-0.28 (0.046)	-0.14 (-0.26, -0.03)	0.0134
	STT	1.74 (0.330)	2.07 (0.358)	0.33 (-0.52, 1.19)	0.4409
	Total CSS	-0.25 (0.121)	-0.71 (0.125)	-0.46 (-0.76, -0.15)	0.0035
Symptom	EDS	-12.5 (1.758)	-17.7 (1.843)	-5.24 (-9.58, -0.90)	0.0181
	TOTAL OSDI	-3.95 (0.892)	-3.65 (0.947)	0.30 (-1.90, 2.50)	0.7897
	VR_OSDI	-0.13 (0.044)	-0.15 (0.048)	-0.02 (-0.13, 0.09)	0.7317
	ODS	-0.41 (0.075)	-0.61 (0.074)	-0.20 (-0.38, -0.02)	0.0340

OPUS-2

	Parameters	Placebo (N = 350)	LIF 5.0% (N = 328)	Difference in LSM (95% CI)	P-value
Sign	ICSS	-0.74 (0.051)	-0.79 (0.051)	-0.05 (-0.18, 0.08)	0.4636
	Nasal CLGSS	-0.30 (0.043)	-0.27 (0.044)	0.03 (-0.08, 0.14)	0.6110
	STT	2.15 (0.302)	2.42 (0.319)	0.27 (-0.54, 1.09)	0.5091
	Total CSS	-1.56 (0.112)	-1.73 (0.112)	-0.18 (-0.47, 0.12)	0.2376
Symptom	EDS	-24.0 (1.588)	-37.7 (1.548)	-13.7 (-17.8, -9.62)	<.0001
	TOTAL OSDI	-8.37 (1.027)	-15.1 (0.984)	-6.75 (-9.37, -4.13)	<.0001
	VR_OSDI	-0.28 (0.051)	-0.61 (0.049)	-0.33 (-0.47, -0.20)	<.0001
	ODS	-0.61 (0.065)	-0.98 (0.061)	-0.38 (-0.54, -0.21)	<.0001
	EDisS	-17.8 (1.575)	-28.7 (1.467)	-11.0 (-14.9, -7.03)	<.0001

The MMRM model used an unstructured covariance matrix to account for correlated measurements within patient and included the fixed effects for treatment, visit, actual baseline values, strata, and the interaction terms of treatment by visit.

Reference ID: 3938302

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

/s/

SOLOMON CHEFO
05/27/2016

YAN WANG
05/27/2016
I concur.

TSAE YUN D LIN
05/27/2016

Statistics Filing Checklist for NDA – 208073 Re-Submission

NDA Number:	208073
NDA Type:	Re-Submission to Complete Response Letter
Drug Name:	Xiidra (Lifitegrast 5.0 % ophthalmic solution)
Indication:	Treatment of the signs and symptoms of dry eye disease (DED)
Applicant:	SHIRE DEVELOPMENT LLC
Stamp Date:	January 22, 2016
Reviewer:	Solomon Chefo

1. Brief Summary of Controlled Clinical Trial(s)

The sponsor (Shire, LLC) developed Lifitegrast ophthalmic solution, 5.0 % for the indication of treatment of the signs symptoms of dry eye disease (DED) (b) (4), and submitted the initial New Drug Application (NDA) on 25 February 2015. Efficacy and safety support for the proposed indication was based on a Phase 2 dose-ranging study and two Phase 3 studies (OPUS-1 and OPUS-2). All studies were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild-to-moderate symptoms while the OPUS-2 study enrolled subjects with moderate-to-severe symptoms. The studies were multicenter, randomized, double-masked, vehicle-controlled studies. The Phase 2 study had four study arms (vehicle and lifitegrast arm at 0.1%, 1.0%, and 5.0% concentrations); the phase 3 studies had two study arms (vehicle and the lifitegrast arm at 5.0% concentration). Each study had a total duration of 14 weeks with two weeks placebo (vehicle) run-in period followed by 12 weeks treatment period.

The Phase 2 study defined a single primary efficacy endpoint for sign and the Phase 3 studies defined co-primary efficacy endpoints for sign and for symptom. The primary efficacy sign endpoint in all studies was the same and was based on the inferior corneal staining score (0-4 scale), but the primary symptom endpoints for OPUS-1 and OPUS-2 varied: the primary symptom endpoint for OPUS-1 was based on the visual-related function subscale of the Ocular Surface Disease Index (0-4 scale) while the primary symptom endpoint for OPUS-2 was based on the eye dryness score (EDS) of the visual analogue scale (0-100 scale) which was selected based on results from a subgroup of patients from OPUS-1 study.

The Phase 3 studies did not demonstrate consistent efficacy results: OPUS-1 showed a statistically significant treatment effect for the primary sign endpoint ($p=0.0007$), but not for the primary symptom endpoint ($p=0.8261$) whereas OPUS-2 showed a statistically significant treatment effect for the primary symptom endpoint ($p<0.0001$), but not for the primary sign endpoint ($p=0.6122$). The Phase 2 study showed a dose-response and supportive treatment effect for the primary sign as well as for the two symptom endpoints. Consequently, the statistical review concluded that there is a lack of substantial evidence to support Xiidra for the proposed indication of treatment of the signs and symptoms of DED, and recommended that an adequate and well controlled study be conducted to provide additional efficacy data (the statistical review for this NDA application is posted in DARRTs - see entry 07/22/2015).

Reference ID: 3886386

At the conclusion of the Agency's review of the lifitegrast NDA, the sponsor received a Complete Response Letter (CRL) from the Agency on 16 October 2015. In the CRL, the Agency requested that an additional clinical trial be conducted to provide substantial evidence of efficacy of the drug product in the intended patient population.

The need for an additional clinical trial was also discussed during the initial Pre-NDA meeting held on 15 May 2015 after preliminary efficacy results were presented. Following the initial Pre-NDA meeting, the sponsor initiated a Phase 3, multicenter, randomized, double-masked, and placebo controlled study comparing lifitegrast 5.0% to placebo administered twice daily for 84 days (referred to as OPUS-3). The sponsor indicated that OPUS- 3 was designed similar to OPUS-2 and included patients with dry eye with a recent history of artificial tear use within 30 days of study entry and an eye dryness score (EDS) ≥40 at baseline. Unlike OPUS-2 which evaluated a co-primary efficacy endpoint for sign and symptom of dry eye, OPUS-3 evaluated a single primary efficacy endpoint for the symptoms of dry eye as measured by the mean change from Baseline to Day 84 in EDS. The mean changes from baseline in EDS at Days 42 and 14 were also assessed as key secondary endpoints in the study. The sponsor treated the signs of dry eye conditions (as measured by the inferior corneal staining score) as a safety variable in the study.

On 18 November 2015, the sponsor requested a Type A End-of Review Meeting with the objective to provide the Agency a summary of the OPUS-3 topline results (indicating the study met the primary and key secondary endpoints) and to provide their resubmission application format and content intended to address the deficiencies listed in the CRL to support approval.

In the 8 December 2015 preliminary Written Comments, the Agency requested that the results for the sign assessments be discussed in the OPUS-3 study report despite being defined in the study as a safety variable; with that in mind, the Agency agreed with the planned format and content of the resubmission to address the deficiencies in the CRL to support review.

On January 22 the sponsor re-submitted NDA application for lifitegrast for the treatment of the signs and symptoms of DED (b) (4) administered twice a day (b) (4)) into each eye. The re-submission included efficacy and safety results from a single Phase 3 OPUS-3 study, and as such, the filing review summarized below applies to this study only.

It should be noted that the overall conclusion for demonstration of substantial evidence of efficacy of the drug product for the proposed indication will be based on the totality of evidence seen in the Phase 2, OPUS-1, OPUS-2, and OPUS-3 studies. The statistical review for the initial NDA application covered the Phase 2, OPUS-1, and OPUS-2 studies (See DARRTs entry 07/22/2015).

Reference ID: 3886386

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information from Review of the Protocol and the Study Report

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	☑			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	☑			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			☑	
Appropriate references for novel statistical methodology (if present) are included.			☑	
Safety data organized to permit analyses across clinical trials in the NDA.	☑			
Investigation of effect of missing data and discontinued follow-up on statistical analyses as described by applicant appears adequate.	☑			

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA208073\0019\
Dataset structure (e.g., SDTM or ADaM)	YES
Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	YES
List the dataset(s) that contains the primary endpoint(s)	Dataset name **adef.xpt** and primary efficacy variable **chg** is the primary efficacy variable**.**
Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	NA
Are the define files sufficiently detailed?	NO
Safety data are organized to permit analyses across clinical trials in the NDA.	YES

Reference ID: 3886386

4. Filing Issues

Table 4: Initial overview of the NDA/BLA application for refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	☑			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	☑			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		☑		
Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).	☑			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

Based on our preliminary review, the NDA is fileable.

Reference ID: 3886386

Appendix:

Table 20: Subject Disposition in the Phase 2, OPUS-1, OPUS-2, and OPUS-3 Studies (Randomized Population)

		Phase 2				OPUS-1		OPUS-2		OPUS-3	
		PBO	LIF 0.1%	LIF 1.0%	LIF 5.0%	PBO	LIF 5.0%	PBO	LIF 5.0%	PBO	LIF 5.0%
Randomized		58	57	57	58	295	293	360	358	356	355
ITT Population, n (%)		58 (100.0)	57 (100.0)	57 (100.0)	58 (100.0)	295 (100.0)	293 (100.0)	360 (100.0)	358 (100.0)	356 (100)	355 (100)
Subjects completing study, n (%)		48 (82.8)	54 (94.7)	51 (89.5)	48 (82.8)	284 (96.3)	281 (95.9)	348 (96.7)	321 (89.7)	318 (89.3)	319 (89.9)
Subject withdrawals, n (%)		10 (17.2)	3 (5.3)	6 (10.5)	10 (17.2)	11 (3.7)	12 (4.1)	12 (3.3)	37 (10.3)	38 (10.7)	36 (10.1)
Reason for subject withdrawal, n (%)	Adverse event	1 (1.7)	2 (3.5)	2 (3.5)	6 (10.3)	3 (1.0)	10 (3.4)	3 (0.8)	26 (7.3)	9 (2.5)	22 (6.2)
	Lost to follow-up	2 (3.4)	0	0	1 (1.7)	2 (0.7)	0	0	2 (0.6)	4 (1.1)	2 (0.6)
	Non-compliance	1 (1.7)	0	2 (3.5)	1 (1.7)	2 (0.7)	0	0	1 (0.3)	5 (1.4)	2 (0.6)
	Pregnancy	0	0	0	0	1 (0.3)	0	0	0	0	0
	Death	0	0	1 (1.8)[a]	0	0	0	0	0	0	0
	Other	6 (10.3)	1 (1.8)	1 (1.8)	2 (3.4)	3 (1.0)	2 (0.7)	9 (2.5)	8 (2.2)	13 (3.7)	6 (1.7)
	Erroneously admitted	0	0	0	0	0	0	0	0	7 (2.0)	4 (1.1)

ITT=intent-to-treat; LIF=lifitegrast, PBO=placebo
[a] Fatal cardiac arrest assessed by investigator as not treatment-related
Source: Module 5.3.5.3, Table 1.1.1

Reference ID: 3886386

Table 18 Demographics – ITT Populations in the Phase 2, OPUS-1, OPUS-2, and OPUS-3 Studies

		Phase 2 N=230				OPUS-1 N=588		OPUS-2 N=718		OPUS-3 N=711	
		PBO	LIF 0.1%	LIF 1.0%	LIF 5.0%	PBO	LIF 5.0%	PBO	LIF 5.0%	PBO	LIF 5.0%
N		58	57	57	58	295	293	360	358	356	355
Mean age (years)		60.4	63.1	63.6	62.3	61.1	60.2	58.9	58.7	58.6	58.8
Female n (%)		45 (77.6)	47 (82.5)	40 (70.2)	47 (81.0)	217 (73.6)	229 (78.2)	265 (73.6)	285 (79.6)	269 (75.6)	268 (75.5)
AT users n (%)		29 (50.0)	22 (38.6)	27 (47.4)	31 (53.4)	129 (43.7)	128 (43.7)	360 (100)	358 (100)	356 (100)	355 (100)[a]
Race n (%)	White	54 (93.1)	53 (93.0)	53 (93.0)	53 (91.4)	276 (93.6)	270 (92.2)	305 (84.7)	303 (84.6)	279 (78.4)	265 (74.6)
	Non-White	4 (6.9)	4 (7.0)	4 (7.0)	5 (8.6)	19 (6.4)	23 (7.8)	55 (15.3)	55 (15.4)	77 (21.6)	90 (25.4)
Ethnicity n (%)	Hispanic or Latino	0	1 (1.8)	0	0	7 (2.4)	6 (2.0)	64 (17.8)	79 1(22.1)	58 (16.3)	60 (16.9)
	Not Hispanic or Latino	58 (100)	56 (98.2)	57 (100)	58 (100)	288 (97.6)	287 (98.0)	296 (82.2)	279 (77.9)	298 (83.7)	295 (83.1)

AT=artificial tears; ITT=intent-to-treat; LIF=lifitegrast; PBO=placebo
[a] A history of recent artificial tear use was not indicated in the eCRF for Subject 18-010.
Source: Module 5.3.5.3 Table 2.1.1

Reference ID: 3886386

Table 19: Mean Baseline ICSS and EDS in the Phase 2, OPUS-1, OPUS-2, and OPUS-3 Studies (ITT Populations)

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

ICSS (0 – 4 point scale, 0=no staining, 4=coalescent with 0.5 increments; EDS (0 – 100 point scale, 0=discomfort, 100=maximal discomfort)
CAE=controlled adverse environment; EDS=eye dryness score; ICSS=inferior corneal staining score; ITT=intent-to-treat; LIF=lifitegrast, max=maximum; min=minimum; PBO=placebo; SD=standard deviation
Note: Phase 2 and OPUS-1 values are pre-CAE exposure. The CAE was not used in the OPUS-2 and OPUS-3 studies.
[a] ITT population for placebo group included 295 subjects but 1 subject did not have a study eye designated due to a missed visit, therefore n=294 for placebo group in analyses with evaluations of the study eye.
Source: Module 5.3.5.3, Table 2.2.1

Reference ID: 3886386

Efficacy Results for OPUS-3

Table 9: Eye Dryness Score (VAS) – Mean Change from Baseline to Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

	Placebo N=356	Lifitegrast N=355
Baseline, Day 0/Visit 2		
n	356	355
Mean (SD)	69.0 (17.08)	68.3 (16.88)
Change from baseline to Day 84/Visit 5		
n	353	353
Mean (SD)	-30.7 (28.01)	-37.9 (28.85)
Treatment Effect (SE)	7.16 (2.096)	
95% CI for Treatment Effect	3.04, 11.28	
P-value	0.0007	

CI = confidence interval; ITT=intent-to-treat; LOCF = last observation carried forward; SD=standard deviation; SE=standard error; VAS=visual analogue scale
Note: Eye dryness was scored on a VAS from 0-100 (0=no discomfort; 100=maximal discomfort).
Source: Section 14, Table 3.1.1.1

Table 15: EDS (VAS) – Mean Change from Baseline to Day 42 (Week 6) and to Day 14 (Week 2), Separately, in the OPUS-3 Study (ITT population with LOCF)

	PBO N=356	LIF 5.0% N=355
Baseline (Day 0)		
n	356	355
Mean (SD)	68.96 (17.079)	68.31 (16.883)
Change from baseline to Day 42 (Week 6)		
n	353	353
Mean (SD)	-23.92 (25.994)	-33.21 (27.425)
Treatment Effect (SE)	9.32 (1.976)	
95% CI for Treatment Effect	5.44, 13.20	
p value	<0.0001	
Change from baseline to Day 14 (Week 2)		
n	353	352
Mean (SD)	-15.02 (22.397)	-22.86 (25.435)
Treatment Effect (SE)	7.85 (1.792)	
95% CI for Treatment Effect	4.33, 11.37	
p value	<0.0001	

ANOVA=analysis of variance; CI = confidence interval; EDS=eye dryness score; ITT=intent-to-treat; LIF=lifitegrast; LOCF=last observation carried forward; PBO=placebo; SD=standard deviation; SE=standard error; VAS=visual analogue scale
Note: Eye dryness is scored from 0-100 on a visual analogue scale (0=no discomfort; 100=maximal discomfort).
The p-value and treatment effect from OPUS-3 were calculated from ANOVA model of change with treatment, stratum and treatment by stratum interaction; weights were set to stratum size.
Source: Module 5.3.5.3 Table 4.1.13

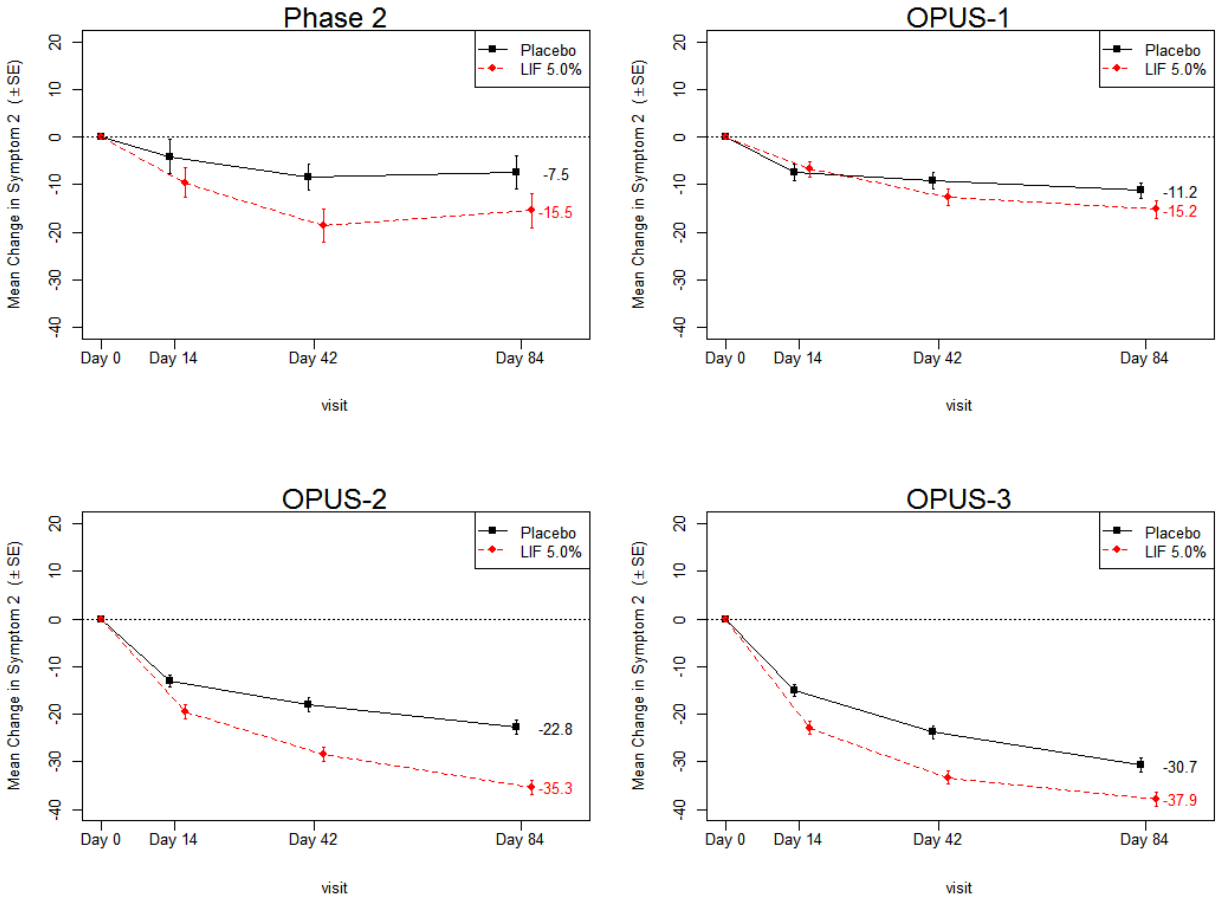
Reference ID: 3886386

Table 17: ICSS in the Study Eye – Mean Change from Baseline to Day 84 in the OPUS-3 Study (ITT Population with LOCF)

	PBO N=356	LIF 5.0% N=355
Baseline (Day 0)		
n	356	355
Mean (SD)	2.46 (0.746)	2.46 (0.681)
Day 84 (Week 12)		
n	351	351
Mean (SD)	1.81 (1.009)	1.66 (1.044)
Change from baseline to Day 84 (Week 12), mean (SD)	-0.64 (0.915)	-0.81 (0.941)
Treatment Effect (SE)	0.17 (0.069)	
95% CI for Treatment Effect	0.03, 0.30	
p-value[a]	0.0144	

CI=confidence interval; ICSS=inferior corneal staining score; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SE=standard error
Note: Corneal staining was scored as follows: 0=no staining/none; 1=occasional/trace; 2=countable/mild; 3=uncountable, but not confluent/moderate; 4=confluent/severe.
[a] P-value from the ANOVA model of change with treatment, stratum, and treatments by stratum interaction; weights were set to stratum size.
Source: Module 5.3.5.3, Table 3.1.1

Summary of Mean Change in EDS over Time across Studies



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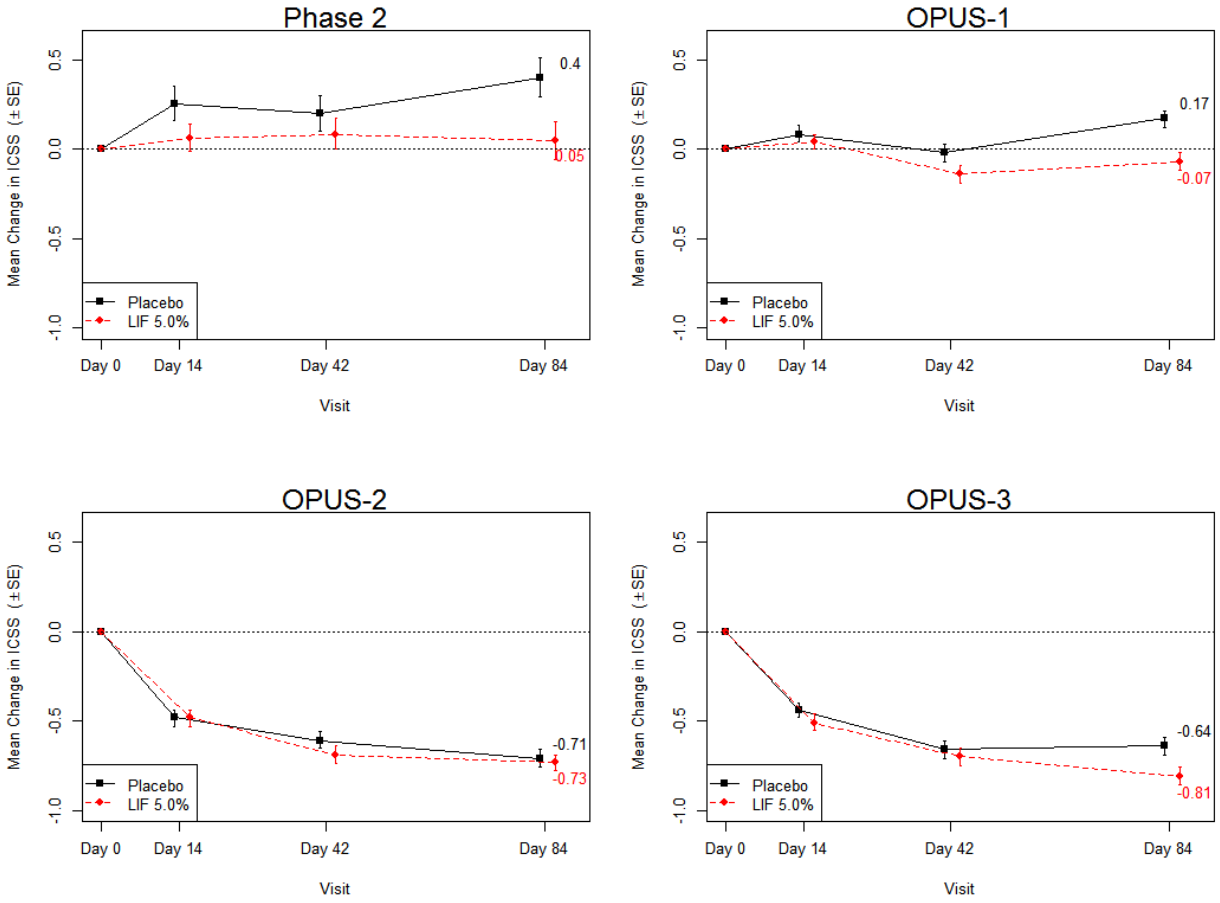
Summary of Mean Change in ICSS over Time across Studies



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SOLOMON CHEFO
02/11/2016

YAN WANG
02/11/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 208073
Drug Name:	Xiidra (Lifitegrast Ophthalmic Solution, 5.0 %)
Indication(s):	For the treatment of signs and symptoms of dry eye disease (b) (4)
Applicant:	SHIRE DEVELOPMENT LLC
Date(s):	Stamp Date: February 25, 2015
	PDUFA Date: October 25, 2015
	Review Date: July 20, 2015
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Solomon Chefo, Ph.D.
Concurring Reviewers:	Yan Wang, Ph.D., Team Leader
Medical Division:	Division of Transplant and Ophthalmology Products
Clinical Team:	Rhea Lloyd, MD, Medical Officer
	William Boyd, MD, Team Leader
Project Manager:	Christina Marshall

Keywords: Clinical Studies, ANCOVA, Dry Eye Disease

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1 EXECUTIVE SUMMARY

The applicant seeks approval of Lifitegrast Ophthalmic Solution (XIIDRA™) 5.0% administered to the ocular surface as a single drop twice daily for the treatment of signs and symptoms of dry eye disease (DED) (b) (4).

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

The three studies were multicenter, randomized, double-masked, placebo-controlled studies conducted in adult subjects with DED and were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild-to-moderate symptom and the OPUS-2 study enrolled subjects with moderate-to-sever symptom. Each study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) - two weeks open label placebo run-in screening period (Day -14 to Day 0) followed by 12 weeks treatment period (Day 0 to 84). Eligible subjects in the Phase 2 study were randomized in a 1:1:1:1 ratio to receive either lifitegrast solution (LIF 0.1%, 1.0%, or 5.0% doses) or Placebo, and in OPUS-1 and OPUS-2 were randomized in a 1:1 ratio to receive either LIF 5.0% or Placebo as a single drop twice daily in each eye for 12 weeks (84 Days).

In each study, efficacy for the treatment of DED was assessed using clinical signs (objective) and symptoms (subjective) of dry eye. The primary sign efficacy endpoint in each study was based on the inferior corneal staining score (ICSS): ICSS at Day 84 was the primary sign endpoint in the Phase 2 study and the change in ICSS from baseline at Day 84 was the co-primary sign endpoint in the OPUS-1 and OPUS-2 studies. The OPUS-1 and OPUS-2 studies also included co-primary efficacy endpoint for symptom, and the two studies differed in this endpoint: the co-primary symptom endpoint in the OPUS-1 study was the change from baseline in the visual-related function subscale of the Ocular Surface Disease Index (VR_OSDI) score at Day 84, and in the OPUS-2 study was the change from baseline in the eye dryness score (EDS) of the visual analogue scale (VAS) at Day 84.

In the applicant primary efficacy analysis, the primary efficacy sign and symptom variables at Day 84 were compared between the treatment groups using the intent-to-treat (ITT) population with last observation carried forward (LOCF) method for imputing missing data: in the Phase 2 study, analysis of covariance (ANCOVA) model was used to compare the mean ICSS at Day 84 between the treatment groups; in OPUS-1 study, a two sample t-test was used to compare the mean changes in ICSS and in VR_OSDI score at Day 84 between the treatment groups; in the OPUS-2 study, regression analysis (ANOVA) model was used to compare the mean changes in ICSS and in EDS at Day 84 between the treatment groups.

It should be noted that the primary sign endpoint in the Phase 2 study was the actual ICSS at Day 84 while in OPUS-1 and OPUS-2 was the change from baseline in ICSS at Day 84; furthermore, the applicant primary analysis in the Phase 2 study adjusted for the baseline values while the primary analyses in OPUS-1 and OPUS-2 did not adjust for the baseline values. Therefore, for ease of across study assessment, ANCOVA model using the change from baseline value as response variable and the baseline value as covariate was performed by the statistical reviewer for all studies in this review. Note that using the actual or the change from baseline value as a response variable in the ANCOVA model provides the same results for treatment comparison.

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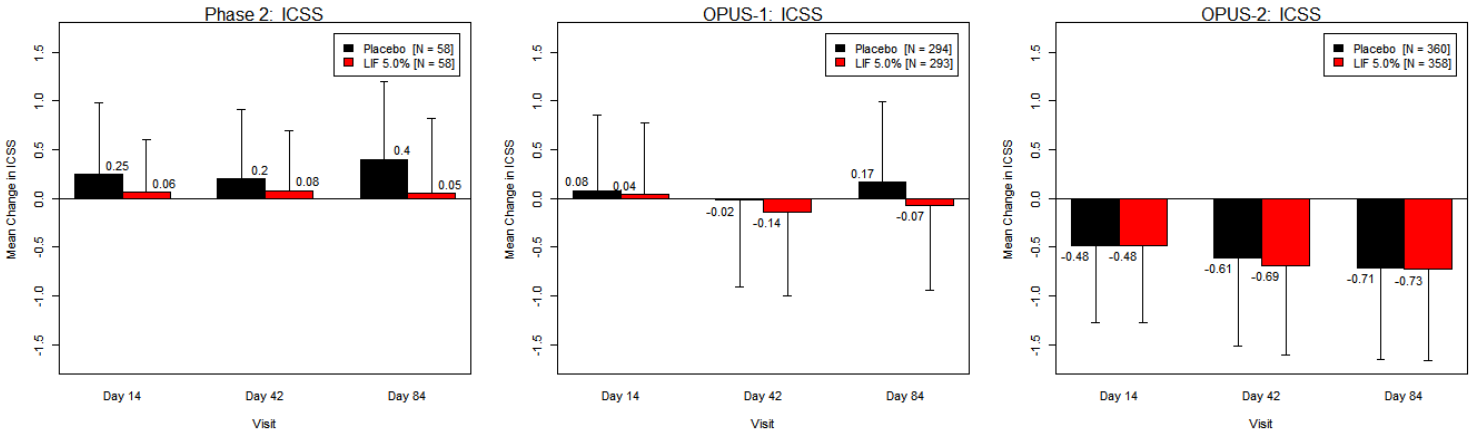
In each study, the majority of patients were Caucasian (≥85%), more than 70% were female, and the average age of patients was about 60 years. Approximately 40-50% of patients in the Phase 2 and in the OPUS-1 study had a recent history of artificial tear use (ATU) whereas all subjects in the OPUS-2 study were required to have a history of ATU. No marked difference was noted in the demographic characteristics between the treatment groups. The key sign and symptom baseline scores were also comparable between the treatment group in each study; however, by study design, the baseline mean ICSS and EDS scores in the OPUS-2 study (for both treatment groups) were much higher than in the Phase 2 and in the OPUS-1 studies (See Table 3).

i) Efficacy results for inferior corneal staining score (ICSS) at Day 84

The primary sign efficacy endpoint in each study was based on ICSS, and the efficacy results for the mean change in ICSS from baseline at each visit are shown in Figure 1 for each study.

Figure 1: Mean Change in ICSS from Baseline at each Visit (Standard Deviation)
(ITT Population, LOCF)



Source: Appendix Table 12

Statistical superiority in improving the clinical sign (as measured using ICSS) was demonstrated in only OPUS-1 study. In the Phase 2 and OPUS-2 studies, on the other hand, LIF 5.0% did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

In OPUS-1 study, LIF 5.0% treated group showed numerically larger mean reduction in ICSS from baseline at Day 84 compared with Placebo. The mean change in ICSS at Day 84 in the LIF 5.0% treated group was -0.07 (95% CI: -0.17, -0.04) and in the Placebo treated group was +0.17 (95% CI: 0.07, 0.26); the treatment difference (*LIF 5.0% minus Placebo*) was -0.23 (95% CI: -0.36, -0.09) and statistical significant difference was achieved in this study (p-value = 0.0007).

In the Phase 2 study, both LIF 5.0% and Placebo did not show mean reduction in ICSS from baseline throughout the study; however, a dose response in the mean change in ICSS was seen at Day 84 (See Figure 9). The mean change in ICSS at Day 84 in the LIF 5.0% treated group was +0.05 (95% CI: -0.16, 0.26) and in the Placebo treated group was +0.40 (95% CI: 0.18, 0.62); the treatment difference was -0.25 (95% CI: -0.51, 0.02) and not statistically significant (p-value = 0.0666). Though not statistically significant, the magnitude of treatment difference in this study (-0.25) was very close to what was seen in OPUS-1 study (-0.23); the non-statistical significant

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result in the Phase 2 study was likely due to smaller sample size compared with OPUS-1 study (note that the p-value in the Phase 2 study was close to 0.05).

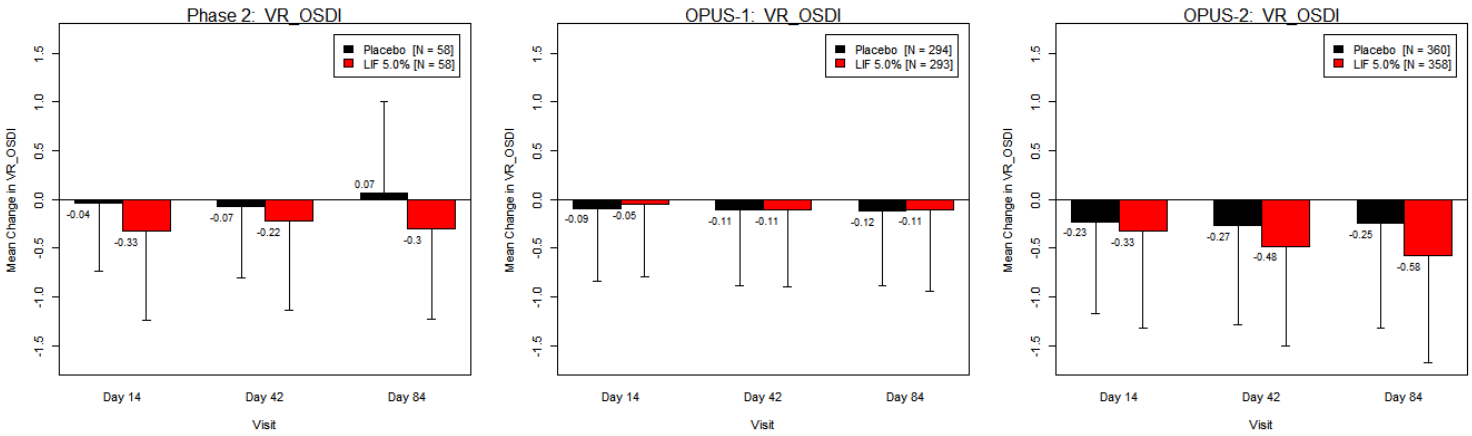
In the OPUS-2 study, both treatment groups showed numerically larger mean reductions in ICSS throughout the study compared with in the Phase 2 and OPUS-1 studies. The mean change in ICSS at Day 84 in the LIF 5.0% treated group in this study was -0.73 (95% CI: -0.83, -0.64) and in Placebo treated group was -0.71 (95% CI: -0.80, -0.61); the treatment difference was -0.03 (95% CI: -0.16, 0.10) and not statistically significant (p-value = 0.6122).

ii) Efficacy results for VR_OSDI score at Day 84

The change in VR_OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study and was supportive symptom endpoint in the Phase 2 and OPUS-2 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-2 studies were intended for descriptive use.

The efficacy results for the mean change in VR_OSDI score from baseline at each visit are shown in Figure 2 for each study.

Figure 2: Mean Change in VR_OSDI from Baseline at each Visit (Standard Deviation)
(ITT Population, LOCF)



Source: Appendix Table 13

Statistical superiority in improving clinical symptom (using VR_OSDI score) at Day 84 was not demonstrated in OPUS-1 study. In OPUS-2 study, LIF 5.0% treated subjects demonstrated a much larger improvement in VR_OSDI over Placebo and in the Phase 2 study showed a moderate improvement over Placebo. Additionally, a dose response improvement in VR_OSDI was seen at Day 84 (see Figure 11) in the Phase 2 study.

In OPUS-2 study, both treatment groups demonstrated larger mean reductions in VR_OSDI score from baseline throughout the study compared to in the Phase 2 and OPUS-1 studies. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.58 (95% CI: -0.70, -0.47) and in the Placebo treated group was -0.25 (95% CI: -0.36, -0.14); the treatment difference was -0.28 (95% CI: -0.41, -0.14; p-value < 0.0001).

In the Phase 2 study, LIF 5.0% treated group showed numerically slightly larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group. The mean change in VR_OSDI score from baseline at Day 84 in the LIF 5.0% treated group was

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-0.30 (95% CI: -0.56, -0.05) and in the Placebo treated group was +0.07 (95% CI: -0.18, 0.32); the treatment difference was -0.30 (95% CI: -0.63, 0.03; p-value = 0.0712).

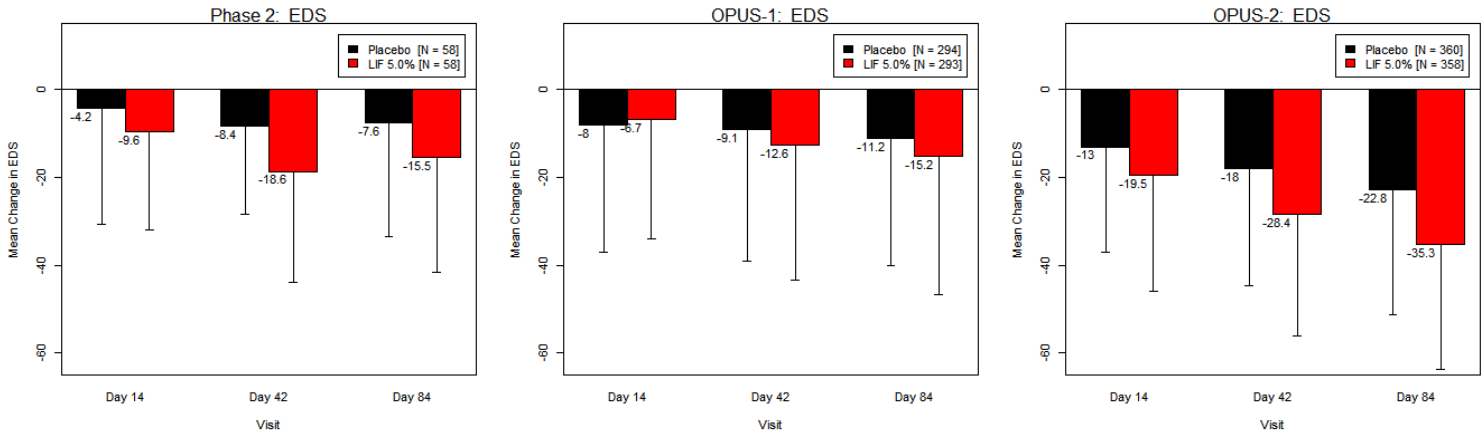
In the OPUS-1 study, both treatment groups showed small and comparable mean reductions in VR_OSDI score from baseline throughout the study. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.11 (95% CI: -0.20, -0.01) and in the Placebo treated group was -0.12 (95% CI: -0.21, -0.04); the treatment difference was -0.01 (95% CI: -0.12, 0.10) and not statistically significant (p-value = 0.8261).

iii) Efficacy results for Eye Dryness Score (EDS) at Day 84

The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2 and was supportive symptom endpoint in the Phase 2 and OPUS-1 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-1 studies were intended for descriptive use.

The efficacy results for the mean change in EDS from baseline at each visit are shown in Figure 3 for each study.

Figure 3: Mean Change in EDS from Baseline at each Visit (Standard Deviation)
(ITT Population, LOCF)



Source: Appendix Table 14

Statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated in OPUS-2 study. Both the Phase 2 and OPUS-1 studies showed numerically better improvement in EDS in the LIF 5.0% treated subjects over Placebo. Additionally, a dose response improvement of EDS was seen at Day 84 (see Figure 13) in the Phase 2 study.

In the OPUS-2 study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.3 (95% CI: -38.3, -32.3) and in the Placebo treated group was -22.8 (95% CI: -25.7, -19.8); the treatment difference was -12.3 (95% CI: -16.4, -8.3) and was strongly statistically significant (p-value < 0.0001).

In OPUS-1 study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.2 (95% CI: -18.8, -11.6) and in the Placebo treated group was -11.2 (95% CI: -14.5, -7.9); the treatment difference was -4.7 (95% CI: -8.9, -0.43; p-value = 0.0311). In this study, a much larger improvement in EDS form baseline at Day 84 was seen in a small subgroup of subjects with a recent history of ATU and with baseline EDS ≥40 (See Figure 31). In this subgroup, the

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mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.4 (95% CI: -43.4, -27.4) and in the Placebo treated group was -22.1 (95% CI: -29.8, -14.4); the treatment difference was -15.3 (95% CI: -25.9, -4.7). Note that the OPUS-2 study was designed based on the positive finding observed in this subgroup and the study used EDS as the primary symptom endpoint.

In the Phase 2 study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.5 (95% CI: -22.6, -8.3) and in the Placebo treated group was -7.6 (95% CI: -14.6, -0.5); the treatment difference was -7.6 (95% CI: -16.8, 1.5; p-value = 0.1021). Note that the confidence interval for the treatment difference did not exclude zero, and this was likely due to the smaller sample size compared to the OPUS-1 study.

Concluding Summary

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

Based on the totality of evidence, the statistical reviewer recommends for additional data from an adequate and well controlled study. The study, at a minimum, is expected to demonstrate statistical superiority of the test product over Placebo in improving a pre-defined clinical symptom. Furthermore, the test product in this study, at a minimum, is expected to show numerically better improvement in ICSS over Placebo or demonstrate similar level of reduction in ICSS seen in the OPUS-2 study.

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2 INTRODUCTION

2.1 OVERVIEW

In this NDA submission, the applicant seeks approval of Lifitegrast Ophthalmic Solution 5.0% (XIIDRA™) for the treatment of signs and symptoms of dry eye disease (DED).

DED is a multifactorial disease of the tears and ocular surface; it occurs when the eye does not produce tears properly, or when the tears are not of the correct consistency and evaporate too quickly. The disease for some people feels like there is a speck of sand in the eye, or stinging or burning that does not go away, and for others, the disease becomes a chronic condition that leads to blurred vision or vision loss if left untreated.

Dry eye is one of the most common of all eye conditions, primarily affecting adults 45 years and older. Many different things can cause dry eye, including environmental exposure, certain medications and medical conditions, eye surgery (such as laser correction surgery), and mainly staring at computer or video screens for too long without blinking.

Despite the prevalence of the disease, there are relatively few treatments available for DED. Current treatments include artificial tears, punctal plugs, and topical cyclosporine. In patients with aqueous tear deficiency, lubricating drops offer temporary relief and provide an important replacement of naturally produced tears. Punctal plug is another treatment option used to plug the drainage holes where tears drain from the eye into the nose.

Cyclosporine (RESTASIS®) is the only drug currently approved by the FDA to treat dry eye; however, it is only indicated for increasing tear production and is not indicated for the treatment of symptoms. Furthermore, it has a long onset of action (24 weeks), and is associated with reduced tolerance due to burning sensations.

The applicant indicated that treatments for DED with faster onset of action that are better tolerated and that can improve both the signs and symptom of the disease remains unmet medical need. To address this unmet medical need, the applicant developed Lifitegrast Ophthalmic Solution for the indication of treatment of signs and symptoms of DED.

2.1.1 Class and Indication

According to the applicant, Lifitegrast ophthalmic solution 5.0% 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 ophthalmic solution 5.0% is indicated for the treatment of the signs and symptoms of dry eye disease (b) (4).

2.1.2 History of Drug Development

The development of lifitegrast ophthalmic solution for the treatment of signs and symptoms of DED was submitted under initial IND (IND 77885) on 21 July 2008. Since then six Type B meetings were held with the Agency to discuss the lifitegrast development program.

The DED clinical development program included five completed and one ongoing randomized, double-masked, placebo-controlled clinical study:

- A Phase 1 dose-escalation study (SAR 1118-001) conducted in 28 healthy volunteers.

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- A Phase 2 dose-ranging study (1118-KCS-100, here after referred to as Phase 2) - a total of 230 subjects with DED were randomized to lifitegrast 0.1%, 1.0%, or 5.0% or placebo (1:1:1:1) and were treated twice daily dosing regimen for 12 weeks (84 days).
- The Phase 2 dry eye study evaluated the efficacy of lifitegrast 0.1%, 1.0%, and 5.0% twice daily. The applicant indicated that the greatest treatment effect was observed with lifitegrast 5.0% twice daily with an acceptable safety profile, and hence this dose regimen was chosen for the Phase 3 studies.
- Two Phase 3 studies (1118-KCS-200 and 1118-DRY-300, here after referred to as OPUS-1 and OPUS-2, respectively) - a total of 588 and 718 subjects were randomized to either lifitegrast 5.0% or placebo (1:1) in OPUS-1 and OPUS-2, respectively, and were treated twice daily dosing regimen for 12 weeks (84 days).
- One long-term multicenter, prospective, randomized, double-masked, placebo-controlled, parallel-arm safety study (1118-DRY-400; referred to as SONATA) - a total of 332 subjects were randomized to either lifitegrast 5.0% or placebo (2:1) and received a twice daily dosing regimen for 1 year (360 days) to compare the safety of lifitegrast 5.0%.
- One ongoing Phase 3, multicenter, randomized, double-masked, placebo-controlled, 12-week study designed to evaluate the safety and efficacy of lifitegrast (OPUS-3). The ongoing study was initiated in November 2014 and the applicant indicated that data from this study will be reported separately.

The study protocols for these studies were initially issued on 05 August 2011 for the Phase 2 study, on 01 June 2009 for OPUS-1 study, and on 05 August 2011 for OPUS-2 study. Each study protocol was subsequently amended one time (Phase 2 study protocol on 01 June 2009, OPUS-1 study protocol on 27 May 2011, and OPUS-2 study protocol on 06 November 2012).

The Phase 2 dose-ranging study and the two Phase 3 studies, OPUS-1 and OPUS-2, were conducted to generate the pivotal efficacy and safety support for the proposed indication.

2.1.3 Specific Studies Reviewed

The submission contains four completed study results: (i) a Phase 2 dose-ranging study and two pivotal Phase 3 studies (OPUS-1 and OPUS-2) to provide efficacy and safety support and (ii) a Phase 3 study (SONATA) to provide safety support for the proposed indication.

The Phase 2, OPUS-1, and OPUS-2 studies were similar in design and all were conducted in the United States (US). Each study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) – two weeks open label placebo run-in screening period followed by 12 weeks treatment period. Treatment in each study was administered as a single drop twice daily (AM and PM) in each eye for 12 weeks. The three studies differed in the use of the controlled adverse environment [1] (CAE) model, proportions of subjects with a history of artificial tear use (ATU), efficacy endpoints, and study population (See more detail in Section 3.2.1).

In the Phase 2 study, a total of 230 subjects were enrolled from five sites all in the US. In this study, the CAE model was used at each scheduled study visits; key inclusion and exclusion criteria during the screening period was based on pre- and post-CAE evaluation while all efficacy analysis during the treatment period was based on the Pre-CAE evaluation. About 50%

[1] The CAE model is a regulated environmental setting aimed at exacerbating the signs and symptoms of dry eye for a fixed period of time.

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of enrolled subjects in this study had a history of ATU within six months prior to the screening visit on Day -14.

In OPUS-1 study, a total of 588 subjects were enrolled from 13 sites all in the US. In this study, CAE model was used during the screening period only (at Days -14 and 0), and key inclusion and exclusion criteria during the screening period was determined based on pre- and post-CAE evaluation. About 55% of enrolled subjects in this study had a history of ATU within six months prior to the screening visit on Day -14.

In OPUS-2 study, a total of 718 subjects were enrolled from 30 sites all in the US. In this study, CAE model was not used throughout the study, and all subjects enrolled in this study had a history of ATU within 30 days prior to the screening visit on Day -14. A brief summary of these pivotal studies are presented in Table 2.

Table 2: Summary of Pivotal Studies Reviewed

Study ID/ Study Type	**Study Design / Primary Study Objective**	**Dose, Route and Regimen/ # of Patients**	**Duration of Treatment / Primary endpoint**	**Study Population**
1118-KCS-100 (Phase 2) Efficacy and Safety	Phase 2, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by inferior corneal staining score (ICSS) measured without use of the CAE at Day 84	Lifitegrast (LIF) 0.1, 1.0, or 5.0% or placebo ophthalmic solution; single drop BID LIF 0.1% (N = 57) LIF 1.0% (N = 57) LIF 5.0% (N = 58) Placebo (N = 58) **Total (N= 230)**	12 Weeks (84 Days) The study included a primary sign efficacy endpoint: **Sign**: inferior corneal fluorescein staining score	• Subjects at least 18 years of age with dry eye disease. • had a history of ATU within six months prior to the screening visit on Day -14 • Subjects with mild-to-moderate symptom
1118-KCS-200 (OPUS-1) Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by change from baseline to Day 84 in ICSS and VR-OSDI and to evaluate safety and tolerability	Lifitegrast (LIF) 5.0% or Placebo ophthalmic solution; single drop BID LIF 5.0% (N = 293) Placebo (N = 295) **Total (N = 588)**	12 Weeks (84 Days) The study included co-primary efficacy endpoints: (i) **Sign**: inferior corneal fluorescein staining score and (ii) **Symptom**: visual-related function Ocular Surface Disease Index subscale (VR_OSDI) score	• Subjects at least 18 years of age with dry eye disease. • Had a history of ATU within six months prior to the screening visit on Day -14 • Subjects with mild-to-moderate symptom
1118-DRY-300 (OPUS-2) Efficacy and Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. / To evaluate efficacy as assessed by change from baseline to Day 84 in ICSS and eye dryness score, and to evaluate safety and tolerability	Lifitegrast (LIF) 5.0% or Placebo ophthalmic solution; single drop BID LIF 5.0% (N = 358) Placebo (N = 360) **Total (N = 718)**	12 Weeks (84 Days) The study included co-primary efficacy endpoints: (i) **Sign**: inferior corneal fluorescein staining score and (ii) **Symptom**: Eye Dryness Score (EDS) [0–100 point visual analogue scale (VAS) in both eyes]	• Subjects at least 18 years of age with dry eye disease. • Had a history of ATU within 30 days prior to the screening visit on Day -14 • Subjects with moderate-to-severe symptom (EDS ≥40)

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Study ID/ Study Type	Study Design / Primary Study Objective	Dose, Route and Regimen/ # of Patients	Duration of Treatment / Primary endpoint	Study Population
1118-DRY-400 (SONATA) Safety	Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study	Lifitegrast 5.0% or placebo ophthalmic solution; single eye drop BID LIF 5.0% (N = 221) Placebo (N = 111) **Total (N = 332)**	360 days (1 year) To evaluate safety as assessed by ocular and non-ocular adverse events	Subjects at least 18 years of age with dry eye disease.

Source: Applicant's Section 2.7.6 Synopsis of Individual Studies

2.2 DATA SOURCES

The data source for this review included the clinical study reports, the analysis and tabulation datasets, and the integrated summary of safety datasets. These were provided in electronic submission and are located at \\cdsesub1\evsprod\nda208073.

The data analyzed in this review were based on the Phase 2 dose-ranging study and the two Phase 3 studies submitted as the pivotal evidence to support the safety and efficacy of lifitegrast 5.0% ophthalmic solution. A high level safety summary was also provided based on the individual studies safety data and based on data from the single Phase 3 safety study (SONATA); a comprehensive safety evaluation is primarily covered in the FDA clinical review.

3 STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The NDA was provided in an electronic submission. It included, among other documents, the clinical study report for each study, the finalized protocols (including amendments) and the statistical analysis plans, both analysis and tabulation datasets, and case report forms for few selected subjects. The SAS codes used to perform the analyses and to create the analysis datasets were also provided.

There were no issues identified with respect to the quality and integrity of the submitted data. Although the submitted datasets were not fully CDISC compliant, the submission included certain elements of the CDISC standards. In addition, the '*Reviewer's Guide Document'* and the '*Define.pdf*' files included in the submission package provided sufficient detail to access and to easily work with the datasets.

Therefore, minimal efforts were needed and no additional support was required from other sources to process the data.

3.2 EVALUATION OF EFFICACY

3.2.1 Study Design and Endpoints

i) Study Design

Efficacy support for lifitegrast ophthalmic solution for the treatment of signs and symptoms of dry eye disease was based on three adequate and well controlled studies; a Phase 2 dose-ranging study (Phase 2) and two Phase 3 studies (OPUS-1 and OPUS-2).

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The three studies were multicenter, randomized, double-masked, placebo-controlled studies conducted in adult subjects with DED and were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild to moderate symptom while the OPUS-2 study enrolled subjects with moderate to severe symptoms. Additionally, CAE model was used in both the Phase 2 and OPUS-1 studies to determine key eligibility criteria while the OPUS-2 study was conducted without the use of the CAE model.

Each study was 14 weeks in duration with five study visits (at Days -14, 0, 14, 42, and 84) - two weeks open label placebo run-in screening period (Day -14 to Day 0) followed by 12 weeks treatment period (Day 0 to 84). CAE model was introduced at all study visits in the Phase 2 study and at the screening visits (on Days -14 and 0) in the OPUS-1 study.

Treatment in each study was administered to the ocular surface as a single drop twice daily (AM and PM) in each eye for 12 weeks (84 Days).

The number subjects with dry eye that were enrolled in each study along with the respective study period are shown in table below:

Studies	**Number Enrolled/ Number of sites**	**Study Period** [1]
Phase 2	230 / 5	08/03/2009 to 02/18/2010
OPUS-1	588 / 13	08/29/2011 to 04/28/2012
OPUS-2	718 / 30	12/07/2012 to 10/01/2013

[1] First subject's consent to last subject's last protocol-defined assessment

The three studies shared some common inclusion criteria; the following were the common study inclusion criteria shared by these studies:

i) Male and Female subjects at least 18 years of age at the time of enrollment

ii) Subject with reported history of dry eye in both eyes

iii) Corneal fluorescein staining score of ≥2 in at least one eye at Days -14 and 0 (based on Pre-CAE score in the Phase 2 and OPUS-1 studies).

iv) Conjunctival redness score ≥1 in at least one eye at Days -14 and 0 (based on Pre-CAE score in the Phase 2 and OPUS-1 studies).

Furthermore, a positive response in at least one eye, defined as meeting all of the following criteria in the same eye was required for eligibility in the Phase 2 and OPUS-1 studies. In these studies, the worst eye that met these requirements was designated as the **study eye**.

- Change from pre-CAE to post-CAE in ICSS ≥ +1
- Ocular discomfort score (ODS) of ≥3 at two consecutive time points (or score of 4 at 2 consecutive time points if the pre-CAE score = 3 at the same visit)
- Schirmer Tear Test score (STT) without anesthesia of ≥1 mm and ≤10 mm.

In the OPUS-2 study, a positive response was defined as meeting ICSS ≥0.5 and STT score of ≥1 mm and ≤10 mm in the same eye at both Days -14 and 0; in this study, the worst eye (highest score) that met these requirements was designated as the **study eye**.

Recent artificial tear use for dry eye (within 30 days prior to Day -14) and EDS ≥40 at Days -14 and 0 were additional eligibility requirements unique in the OPUS-2 study.

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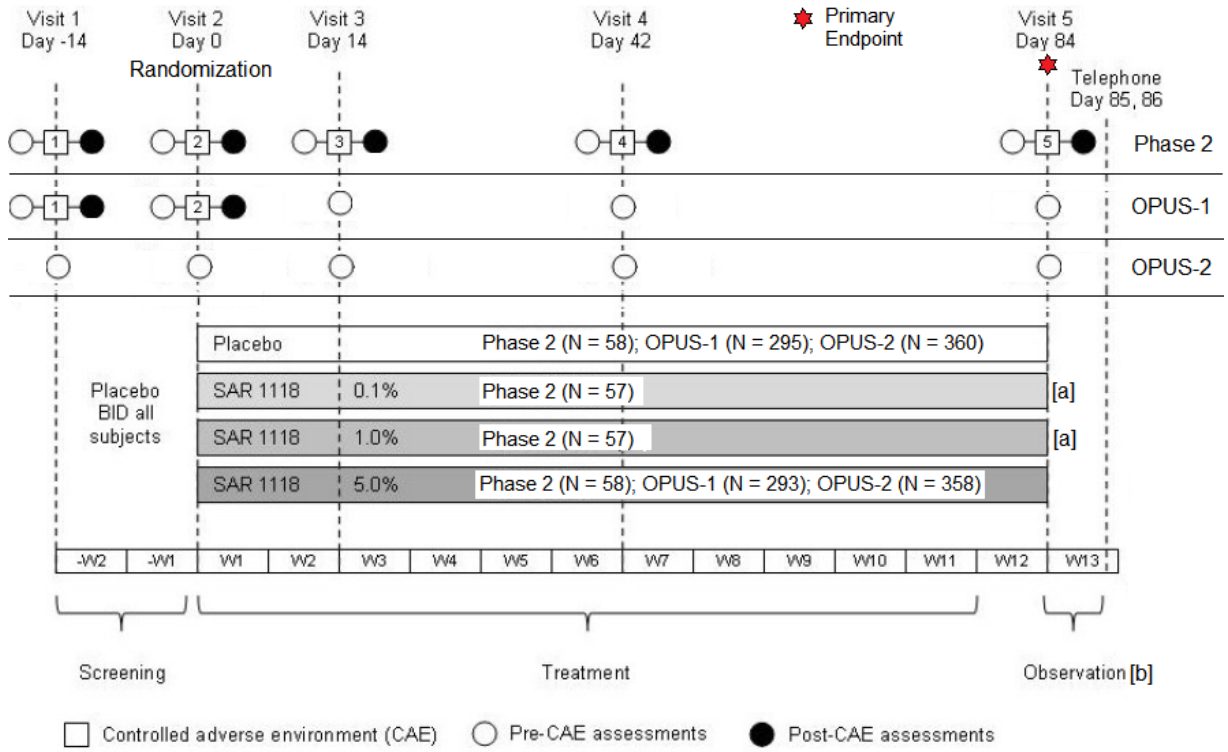
In the three studies, subjects that met all the study specific inclusion and none of the exclusion criteria entered the treatment period, and were randomized at Day 0 to receive either lifitegrast ophthalmic solution or placebo as a single eye drop twice daily in each eye for 84 days.

In the Phase 2 study, eligible subjects were randomized in a 1:1:1:1 ratio to receive either lifitegrast ophthalmic solution (LIF 0.1%, 1.0%, or 5.0%) or Placebo; and in OPUS-1 and OPUS-2, eligible subjects were randomized in a 1:1 ratio to receive either LIF 5.0% or Placebo.

Randomization in the OPUS-1 study was stratified by the Pre-CAE ICSS data in the study eye at Day 0 (≤ 1 versus >1) and by the prior use of artificial tears (Yes versus No). In OPUS-2 study, randomization was stratified by the ICSS data (≤ 1 versus >1) and EDS data (< 60 versus ≥60) in the study eye at Day 0.

In Figure 4 flowchart of each study designs is shown.

Figure 4: Flowchart of Study Design



[a] Specific to the Phase 2 study; [b] Not applicable in OPUS-2 study
Source: Figure 1 of Applicant's Clinical Overview

In each study, efficacy for the treatment of DED was assessed using clinical signs (objective) and symptoms (subjective) of dry eye. For both signs and symptoms of DED, efficacy data were collected at each study visit.

The key ocular sign parameters measured at all study visits included: corneal fluorescein score (inferior, central, and superior cornea), conjunctival lissamine score (nasal and temporal conjunctiva), and Schirmer Tear Test without anesthesia (mm/5min).

- The three regions of corneal fluorescein staining were scored in 0-4 scale with 0.5 increment (*0 = no staining, 1=Occasional, 2=Countable, 3=Uncountable but not confluent, and 4=Confluent*); the associated scores in OPUS-2 study were labeled slightly different (*0=no*

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staining, 1=few/rare punctate lesions, 2=discrete and countable lesions, 3=lesions too numerous to count but not coalescent, and 4=coalescent). The total corneal fluorescein score was derived as the sum of the three regions (0-12 points).

- The two regions of conjunctival lissamine green staining were also scored in 0-4 scale with 0.5 increments; the scores are labeled the same as the scores for corneal fluorescein staining.
- The schirmer tear test (without anesthesia) measured the tear production based on the length of wetting area (in mm/5 minutes) was recorded for each eye.

The key ocular symptom parameters included: ocular discomfort score (ODS), eye dryness score (EDS) of the 7-item visual analogue scale (VAS), and ocular surface disease index (OSDI).

- The ODS was measured in 0–4 point scale (0=no symptom; 4 = severe discomfort) relative to each eye based on subject-reported symptoms at each study visits
- The EDS was measured in 0-100 point scale (0 = no discomfort; 100=maximal discomfort) across both eyes based on subject-reported symptoms at each study visits.
- The OSDI measured in 0-100 scale (0=normal, 100=sever) was derived from 12 items subject-reported questionnaire recorded retrospectively with a 1-week recall period across both eyes. Each of the 12 items was graded on a 0-4 scale (0=none of the time, 4=all of the time, or N/A=not applicable) with the overall OSDI score converted to 0-100 scale.
- The OSDI has an overall score and three subscale scores (ocular symptoms, vision-related function, and environmental triggers). The visual related OSDI (VR_OSDI) subscale included 4 items (reading, driving at night, use of computer, and watching television) each measured in 0-4 scale; the overall VR_OSDI score was 0-4 mean composite score derived from these items.

ii) Study Endpoints

There are a number of clinically accepted sign and symptom efficacy endpoints for the treatment of signs and symptoms of DED, and applicants are generally expected to pre-specify such endpoints and get concurrence from the Agency beforehand. To make efficacy claim for dry eye indication, the test product was generally expected to demonstrate statistical superiority over placebo (vehicle) in improving a clinical sign and a clinical symptom of dry eye in at least two adequately and well controlled studies.

In this submission, the Phase 2 study included a single primary sign endpoint and the two pivotal Phase 3 studies included co-primary sign and symptom efficacy endpoints. The primary sign efficacy endpoint in each study was based on the inferior corneal staining score (ICSS); the OPUS-1 and OPUS-2 studies also included co-primary efficacy endpoint for symptom, and the two studies differed in this endpoint. Details are discussed below.

a) Phase 2 Study

The primary efficacy sign endpoint in the Phase 2 study was the mean ICSS in the study eye at Day 84 (without use of the CAE). In this study, no primary symptom endpoint was defined. However, a number of sign and symptom efficacy secondary endpoints were defined in the study protocol; the results for these endpoints were presented and discussed in the applicant clinical study report. All the secondary endpoints defined in the Phase 2 study protocol were intended to be exploratory in nature.

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b) Phase 3 Study: OPUS-1

i) *Co-primary Efficacy Endpoint:*

The study included co-primary sign and symptom endpoint:

- The co-primary sign endpoint was the mean change in ICSS from baseline at Day 84 in the designated study eye.
- The co-primary symptom endpoint was the mean change in VR_OSDI score from baseline at Day 84.

ii) Secondary Endpoints:

- The secondary sign endpoint was the mean in Schirmer Tear Test (STT; mm/5 minutes) score at Day 14 and at Day 84.
- The secondary symptom endpoint was the mean change in the Total OSDI score from baseline at Day 14 and at Day 84.

c) Phase 3 Study: OPUS-2

i) Co-primary Efficacy Endpoint:

The study included co-primary sign and symptom endpoint:

- The co-primary sign endpoint was the mean change in ICSS from baseline at Day 84 in the designated study eye.
- The co-primary symptom endpoint was the mean change in EDS from baseline at Day 84.

Note that the applicant symptom co-primary endpoint in this study, unlike in the OPUS-1 study, was based on EDS. In the OPUS-1 study, a positive finding in EDS was seen in the subgroup of subjects with a recent history of ATU and EDS ≥ 40. Consequently, in the OPUS-2 study, the applicant enrolled subjects with a recent history of ATU and with baseline EDS ≥ 40 and used EDS as a co-primary symptom endpoint in the study.

ii) Secondary Endpoints:

- The secondary sign endpoints were the mean change in total corneal fluorescein staining scores (Total CSS) and the mean change in nasal conjunctival lissamine green staining score (Nasal CLGSS) from baseline at Day 84 in the designated study eye.
- The secondary symptom endpoints were the mean change in eye discomfort score (EDisS) of the 7-item VAS and the mean change in ocular discomfort score (ODS) from baseline at Day 84.

Several supporting sign and symptom efficacy endpoints were defined in the Phase 2, OPUS-1, and OPUS-2 study protocols. We defer to the study specific clinical study reports for detail and summary of the supporting efficacy variables.

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3.2.2 Statistical Methodology

i) Phase 2 Study

The primary efficacy analysis in this study was a pairwise comparison between the three concentrations of lifitegrast ophthalmic solution (LIF 0.1%, 1.0%, and 5.0%) against Placebo in the primary sign efficacy endpoint of mean ICSS at Day 84.

The applicant primary efficacy analysis method used Analysis of Covariance (ANCOVA) methodology with ICSS at Day 84 as the response variable, and treatment, site, and the baseline ICSS as covariate. To compare the three lifitegrast doses against placebo in the mean ICSS, the applicant used Dunnett's test at two-sided alpha level of 5%.

The primary analysis was performed in the ITT population (defined below) using the last observation carried forward (LOCF) method for imputing missing data. All the secondary sign and symptom efficacy endpoints were analyzed in a similar manner as in the primary efficacy endpoint. Since the secondary endpoints were intended to be exploratory in nature, no formal correction for multiplicity was performed in this study.

As a supportive analysis, the applicant also used an unadjusted 2-sample t-test and a non-parametric Wilcoxon rank sum test. The applicant also analyzed the change from baseline at Day 84 using the same analysis approach.

Analysis Population

In this study, three analysis populations were defined. The intent-to-treat (ITT) population which included all randomized subjects, the per-protocol (PP) population excluded subjects with any major protocol deviations or with incomplete efficacy data from the analysis, and the safety analysis population (SAF) which included all randomized subjects who received at least 1 dose of study drug.

The ITT population was used for all efficacy analyses. The applicant also performed the primary efficacy analysis using the PP population.

ii) Phase 3: OPUS-1 Study

The primary efficacy analysis in this study compared LIF 5.0% against placebo in the co-primary sign endpoint of the mean change in ICCS from baseline at Day 84 and in the co-primary symptom endpoint of VR_OSDI score from baseline at Day 84.

The applicant's primary efficacy analysis for the mean change in ICSS and in VR_OSDI score from baseline at Day 84 was based on a two-sample t-test in the ITT population (defined below) with LOCF method for imputing missing data.

In the applicant analysis, all the secondary efficacy endpoints were analyzed in a similar manner as in the co-primary efficacy endpoints. Furthermore, the applicant proposed Simes modified Bonferroni procedure to control the Type I error rate across the secondary endpoints within an analysis population if both co-primary endpoints were significant.

Analysis Population

In this study as well, three analysis populations were defined. The ITT and SAF populations were identical and included all randomized subjects who received at least 1 dose of study drug.

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The PP population included all randomized subjects who completed the study with no major protocol violations.

iii) Phase 3: OPUS-2 Study

The primary efficacy analysis in this study compared LIF 5.0% against placebo in the co-primary sing endpoint of the mean change in ICCS from baseline at Day 84 and in the co-primary symptom efficacy endpoint of the mean change in EDS from baseline at Day 84.

The applicant's primary efficacy analysis for the mean change in ICSS and in EDS from baseline at Day 84 was performed using regression analysis (ANCOVA) model in the ITT population (defined below) with LOCF method for imputing missing data. The regression model included treatment, strata, and the interaction between treatment and strata.

In the applicant analysis, all the secondary efficacy endpoints were analyzed in a similar manner as in the co-primary efficacy endpoints. Furthermore, the applicant proposed Hochberg's procedure to control the type I error rate at 5% level across all secondary endpoints if both co-primary endpoints were significant.

Analysis Population

In this study, three analysis populations were defined. The randomized population which included all randomized subjects, and the ITT and SAF populations which included all randomized subjects who received at least 1 dose of study drug. Analyses conducted using the ITT population was based on treatment assigned and analyses conducted using the SAF population was based on treatment received.

In this study, per-protocol analysis population was not defined.

Reviewer's Analysis Approach:

i) Phase 2 Study

- The Phase 2 dose-ranging study was primarily designed to identify the most effective dose for the Phase 3 studies by comparing the mean ICSS score of LIF 0.1%, 1.0%, and 5.0% against Placebo. According to the applicant, the greatest treatment effect with an acceptable safety profile was observed with LIF 5.0%, and subsequently this dose regimen was studied in the two Phase 3 studies. Therefore, in this review, all efficacy analyses for the Phase 2 study compared LIF 5.0% dose group against Placebo without correction for multiple comparison.
- Even though only a single primary sign efficacy endpoint was defined in this study, data for a number of sign and symptom variables were also collected in this study including the co-primary symptom variables (EDS and VR_OSDI) and all the secondary sign and symptom variables defined for the OPUS-1 and OPUS-2 studies. Therefore, for the purpose of across study comparisons, all these variables were also analyzed for the Phase 2 study.
- We should note that, with the exception of the primary sign efficacy variable, all other sign and symptom efficacy variables analyzed for the phase 2 study were intended to be exploratory in nature.

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ii) OPUS-1 and OPUS-2 Studies

The applicant primary analysis approach in the OPUS-1 study used two-sample t-test to compare the treatment groups in the mean change in ICSS and in VR_OSDI score from baseline at Day 84. On the other hand, the applicant primary analyses in the OPUS-2 study used regression analysis (ANOVA model) to compare the treatment groups in the mean change in ICSS and in EDS from baseline at Day 84; in the ANOVA model, treatment, strata, and the interaction between treatment and strata were included as covariates. However, the applicant did not provide any justification for inclusion of the interaction term in the model, and there was also no reason to suspect an interaction effect (based on the applicant analysis method, the p-values for the interaction term was 0.7037 for ICSS and was 0.5782 for EDS).

Overall, the statistical reviewer noted that the three studies differed in the efficacy endpoint definition as well as in the primary efficacy analyses methods:

- The primary sign endpoint in the Phase 2 study was based on the actual ICSS at Day 84 whereas in the OPUS-1 and in the OPUS-2 studies was based on the change from baseline in ICSS at Day 84 and
- The applicant primary analysis in the Phase 2 study adjusted for the baseline values whereas the primary analyses in OPUS-1 and OPUS-2 did not adjust for the baseline values.

Therefore, for ease of across study assessment, the statistical reviewer primary analysis approach (for all the studies) used ANCOVA model based on the ITT population with LOCF for missing data. In the ANCOVA model, the change from baseline value at Day 84 was used as the response variable, and treatment, baseline value, and the study specific strata (specific for OPUS-1 and OPUS-2) were used as covariates. Note that using the actual value or the change from baseline value as a response variable in the ANCOVA model provides the same results for treatment comparison.

Based on the ANCOVA model, the difference in the mean change between the treatment groups was determined using the Least Square Means (LS Means). The default observed margin (OM) option in the LSMEANS statement of the PROC MIXED procedure in SAS was used to account for any imbalance in sample size and in the mean change values across strata.

As sensitivity analyses, the statistical reviewer also performed ANCOVA analysis using observed data (without missing data imputation) and unadjusted analysis using a two sample t-test and a non-parametric Wilcoxon rank sum test. Furthermore, a mixed model repeated measure (MMRM) analysis that accounted for correlated measurements was also performed using the observed data; the model used an unstructured covariance matrix to account for correlated measurements within patient and included the fixed effects for treatment, visit, actual baseline values, strata, and the interaction terms of treatment by visit. Treatment difference in the mean change from baseline at each visit was determined based on LS Means using the MMRM analysis.

Overall, the same efficacy conclusion was reached based on the applicant and the reviewer analyses methods. Furthermore, the sensitivity analyses and the MMRM analysis results were consistent with the primary efficacy analysis results.

Reference ID: 3795926

3.2.3 Patient Disposition, Demographics, and Baseline Disease Characteristics

Overall, 230, 588, and 718 patients were randomized in the Phase 2 (including all doses), OPUS-1, and OPUS-2 studies, respectively. Note that the results in Table 1 for patient disposition, in Table 2 for demographic summary, and in Table 3 for baseline disease characteristics only included LIF 5.0% for the Phase 2 study.

3.2.3.1 Patient Disposition

The summary of patient disposition and the primary reasons for study discontinuation during the 12-week treatment period in each study are shown in Table 1 below.

Table 1: Disposition of Patients and Reasons for Study Discontinuation
(All Randomized Subjects)

	Phase 2		OPUS-1		OPUS-2	
	Placebo (N = 58)	LIF 5.0% (N = 58)	Placebo (N = 295)	LIF 5.0% (N = 293)	Placebo (N = 358)	LIF 5.0% (N = 360)
Number of randomized subjects (ITT Population)	58 (100.0)	58 (100.0)	295 (100)	293 (100)	358 (100.0)	360 (100.0)
Safety Population	58 (100.0)	58 (100.0)	295 (100)	293 (100)	359 (99.7)	359 (100.3)
Per-protocol Population	44 (75.9)	46 (79.3)	265 (89.8)	246 (84.0)	NA	NA
Subjects who completed the study	48 (82.8)	48 (82.8)	284 (96.3)	281 (95.9)	348 (96.7)	321 (89.7)
Subjects discontinued from the study	10 (17.2)	10 (17.2)	11 (3.7)	12 (4.1)	12 (3.3)	37 (10.3)
Reason for withdrawal						
Adverse event	1 (1.7)	6 (10.3)	3 (1.0)	10 (3.4)	3 (0.8)	26 (7.3)
Lost to follow-up	2 (3.4)	1 (1.7)	2 (0.7)	0	0	2 (0.6)
Non-compliance	1 (1.7)	1 (1.7)	2 (0.7)	0	0	1 (0.3)
Pregnancy	0	0	1 (0.3)	0	0	0
Other	6 (10.3) [b]	2 (3.4) [a]	3 (1.0)	2 (0.7)	9 (2.5)	8 (2.2)

Source: Table 3 of Phase 2, OPUS-1, and OPUS-2 Clinical Study Reports. LIF 5.0% = lifitegrast 5.0% ophthalmic solution
[a] withdrew consent; [b] non-compliance due to disallowed medications

Of the 230 randomized subjects in the Phase 2 study, a total 29 (13%) subjects discontinued from the study; 10 (17%) subjects each discontinued from the LIF 5.0% and Placebo treated group before Week 12. Adverse event (AE) was the most common reason for discontinuation in the LIF 5.0% treated group (about 10% versus 2.0% in placebo) while non-compliance due to disallowed medications was the most common reason for discontinuation in the Placebo treated group (about 10%). One subjects in the placebo treated group discontinued due to non-ocular AE (due to sinus pressure and sinus infection) while all six subjects in the LIF 5.0% treated group discontinued due to ocular AE (*due to ocular infection, ocular pain, burning or stinging upon instillation of study drug, irritated eyelids, excess ocular tearing, or ocular redness*).

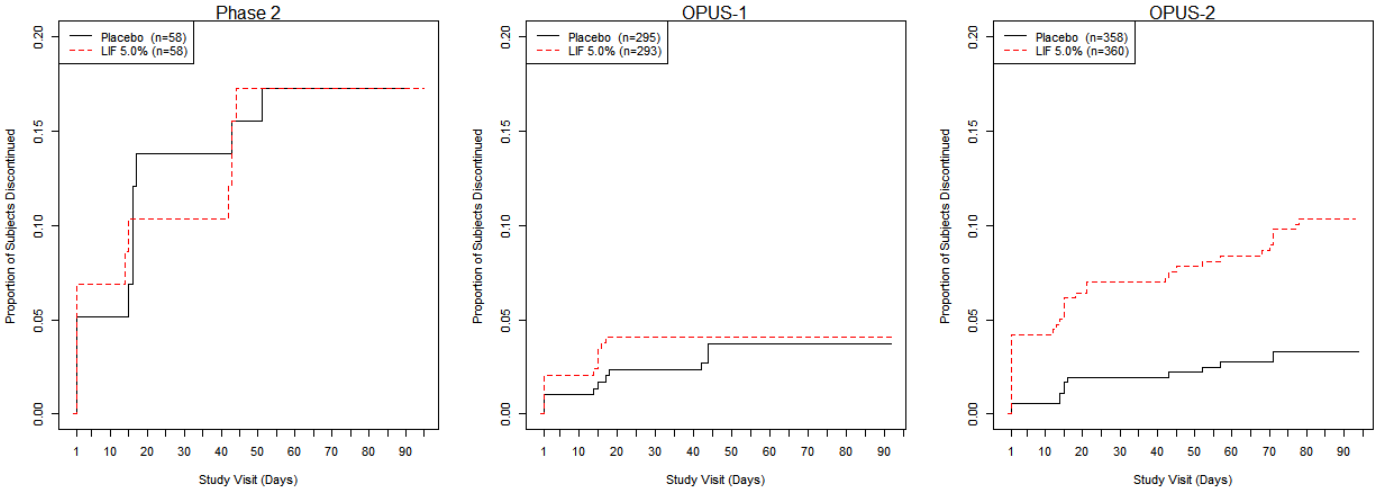
Of the 588 randomized subjects in OPUS-1 study; a total of 23 (4%) subjects discontinued from the study before Week 12; the discontinuation rates were comparable between the treatment groups. Adverse event was the most common reason for discontinuation in the LIF 5.0% treated group (3% versus 1% in Placebo). In the Placebo treated group, three subjects discontinued due to AE (*due to worsening of depression, eye pain, or increased central superficial punctate keratitis*). In the LIF 5.0% treated group, most of the discontinued subjects due to AE did so due to *burning, stinging, or blurred vision upon instillation of study drop*.

Reference ID: 3795926

Of the 718 randomized subjects in OPUS- 2 study; a total of 49 (7%) subjects discontinued from the study before week 12; the discontinuation rate in the LIF 5.0% treated group was three times higher than in the placebo treated group (10% versus 3% in Placebo). Adverse event was the most common reason for discontinuation in the LIF 5.0% treated group (7% versus 1.0% in Placebo). In the LIF 5.0% treated group, approximately half of the discontinued subjects due to AE did so because of *blurred vision and burning upon investigational product instillation*.

The proportions of subjects discontinued in each study over time during the 12-week treatment period are shown in Figure 5. In the Phase 2 and OPUS-1 study, the discontinuation rate over time was comparable between the treatment groups. In the OPUS-2 study, on the other hand, the discontinuation rate at all visits were much higher in the LIF 5.0% treated group compared with in the Placebo treated group, and about half of the discontinued subjects in this group did so early on (before Day 42) in the study.

Figure 5: Proportion of Subjects Discontinued from Study
(All Randomized Subjects)



3.2.3.2 Demography

The summary of demographic and baseline characteristics for subjects in the ITT population are presented in Table 2.

In each study, the majority of patients were Caucasian (≥85%), more than 70% were female, and the average age of patients was about 60 years with 30-40% of patients at least 65 years old. The majority of subjects in each study had blue or brown iris color (≥ 65%).

Approximately 50% of subjects in the Phase 2 study and 44% of subjects in the OPUS-1 study had a history of artificial tear use whereas all subjects in the OPUS-2 study had a history of artificial tear use since it was one of the study inclusion criteria.

In each study, no marked difference between the treatment groups was observed in terms of the demographic characteristics.

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Table 2: Demographic Summary by Study and Treatment Group
(ITT Population)

	Phase 2		OPUS-1		OPUS-2	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 358)**	**LIF 5.0% (N = 360)**
Age						
Mean (SD)	60.4 (12.93)	62.3 (12.22)	61.1 (11.77)	60.2 (12.21)	58.9 (14.26)	58.7 (13.93)
Median	60.5	62.0	62.0	59.0	60.5	59.4
Range	26.0, 89.0	31.0, 85.0	24.0, 85.0	20.0, 91.0	19.8, 88.7	19.2, 97.5
Age Group, n (%)						
< 65	40 (69.0)	35 (60.3)	178 (60.3)	194 (66.2)	225 (62.5)	236 (65.9)
>= 65	18 (31.0)	23 (39.7)	117 (39.7)	99 (33.8)	135 (37.5)	122 (34.1)
Sex, n (%)						
Female	45 (77.6)	47 (81.0)	217 (73.6)	229 (78.2)	265 (73.6)	285 (79.6)
Male	13 (22.4)	11 (19.0)	78 (26.4)	64 (21.8)	95 (26.4)	73 (20.4)
Ethnicity, n (%)						
Hispanic or Latino	0 (0.0)	0 (0.0)	7 (2.4)	6 (2.0)	64 (17.8)	79 (22.1)
Not Hispanic or Latino	58 (100)	58 (100)	288 (97.6)	287 (98.0)	296 (82.2)	279 (77.9)
Race, n (%)						
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	2 (0.6)	4 (1.1)
Asian	1 (1.7)	3 (5.2)	2 (0.7)	3 (1.0)	14 (3.9)	19 (5.3)
Black or African American	3 (5.2)	2 (3.4)	11 (3.7)	16 (5.5)	34 (9.4)	30 (8.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)	2 (0.6)
White	54 (93.1)	53 (91.4)	276 (93.6)	270 (92.2)	305 (84.7)	303 (84.6)
Other	0 (0.0)	0 (0.0)	4 (1.4)	3 (1.0)	2 (0.6)	0 (0.0)
Iris Color, n (%)						
Black	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	1 (0.3)
Blue	20 (34.5)	21 (36.2)	98 (33.2)	105 (35.8)	86 (23.9)	80 (22.3)
Brown	21 (36.2)	18 (31.0)	96 (32.5)	113 (38.6)	189 (52.5)	193 (53.9)
Gray	1 (1.7)	1 (1.7)	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)
Green	6 (10.3)	3 (5.2)	27 (9.2)	18 (6.1)	35 (9.7)	27 (7.5)
Hazel	10 (17.2)	15 (25.9)	71 (24.1)	52 (17.7)	49 (13.6)	56 (15.6)
Other: Blue/Brown	--	--	0 (0.0)	1 (0.3)	--	--
Missing	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	--	--
Artificial Tear Use, n (%) [1]						
No	29 (50.0)	27 (46.6)	165 (55.9)	165 (56.3)	0 (0.0)	0 (0.0)
Yes	29 (50.0)	31 (53.4)	130 (44.1)	128 (43.7)	360 (100)	358 (100)

Source: Table 4 of Phase 2, OPUS-1, and OPUS-2 Clinical Study Reports; [1] Based on reviewer analysis

3.2.3.3 Baseline Disease Characteristics

The descriptive summary for the key baseline sign and symptom variables are shown in Table 3; furthermore, the distributions for the sign variables are shown in Figure 6 and Figure 7 and for the symptom variables are shown in Figure 8. Overall, the baseline scores for the key sign and symptom variable were comparable between the treatment groups.

In the Phase 2 and OPUS-1 study, the mean baseline ICSS was about 1.8 and about 65% of subjects within each study had baseline ICSS >1.5; by design, the maximum baseline ICSS score in these studies was ≤ 3.0. In the OPUS-2 study, on the other hand, the mean baseline ICSS was slightly higher than in the Phase 2 and in OPUS-1 studies; in this study, the mean baseline ICSS was about 2.4 and about 85% of subjects in this study had baseline ICSS >1.5. Similar patterns were observed at baseline when sign was assessed using Total CSS, Nasal CLGSS, and STT.

For the key symptom variables, the mean baseline EDS in 0-100 scale (0 = no discomfort; 100=maximal discomfort) was about 52 in the Phase 2 study, about 40 in OPUS-1, and about 69 in OPUS-2; and about 38% of subjects in the Phase 2 study, 25% of subjects in OPUS-1, and

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67% of subjects in OPUS-2 had EDS ≥ 60 at baseline. Note that OPUS-2 study enrolled more symptomatic subjects by design (i.e., EDS ≥40 at baseline was required for eligibility). Similar patterns were observed at baseline when symptom was assessed using ODS, VR_OSDI, and Total OSDI scores.

Table 3: Baseline Disease Characteristics by Study and Treatment Group
(ITT Population)

Parameters	Phase 2		OPUS-1		OPUS-2	
	Placebo (N = 58)	LIF 5.0% (N = 58)	Placebo (N = 295)	LIF 5.0% (N = 293)	Placebo (N = 358)	LIF 5.0% (N = 360)
Key Sign Parameters						
ICSS:						
Mean	1.6 (0.51)	1.8 (0.51)	1.8 (0.60)	1.8 (0.60)	2.4 (0.72)	2.4 (0.76)
Median	2.0	2.0	2.0	2.0	2.5	2.5
Range	0.5, 2.5	0.5, 3.0	0.5, 3.0	0.5, 3.0	0.5, 4.0	0.5, 4.0
ICSS Category, n (%)						
≤ 1.5	22 (37.9)	19 (32.8)	105 (35.7)	95 (32.4)	47 (13.1)	46 (12.8)
> 1.5	36 (62.1)	39 (67.2)	189 (64.3)	198 (67.6)	313 (86.9)	312 (87.2)
Total CSS						
Mean	4.4 (1.20)	4.3 (1.06)	4.8 (1.38)	4.8 (1.40)	5.2 (2.01)	5.1 (2.08)
Median	4.3	4.0	4.5	4.5	4.5	4.5
Range	1.0, 7.0	2.5, 7.5	2.0, 9.5	2.0, 10.0	1.0, 11.5	1.0, 12.0
Nasal CLGSS:						
Mean	1.80 (0.93)	1.69 (0.77)	1.90 (0.84)	2.03 (0.81)	2.14 (1.05)	2.13 (1.04)
Median	2.00	2.00	2.00	2.00	2.50	2.00
Range	0.0, 4.0	0.0, 3.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0
STT (Un-anesthetized):						
Mean	4.7 (2.84)	5.0 (2.98)	4.7 (2.86)	4.9 (3.01)	5.1 (2.77)	5.5 (2.83)
Median	4.0	5.0	4.0	4.0	5.0	5.0
Range	1.0, 10.0	1.0, 10.0	1.0, 10.0	1.0, 10.0	0.0, 10.0	1.0, 10.0
Key Symptom Parameters						
EDS:						
Mean	51.8 (23.55)	51.6 (24.69)	41.6 (29.69)	40.2 (28.64)	69.2 (16.76)	69.7 (16.95)
Median	55.0	51.0	39.0	42.0	69.0	69.0
Range	0.0, 98.0	3.0, 100.0	0.0, 100.0	0.0, 100.0	40.0, 100.0	40.0, 100.0
EDS Category, n (%)						
< 40 [1]	17 (29.3)	19 (32.8)	148 (50.2)	137 (46.8)	NA	NA
40 – 50	7 (12.1)	7 (12.1)	20 (6.8)	28 (9.6)	52 (14.4)	43 (12.0)
50 – 60	11 (19.0)	10 (17.2)	45 (15.3)	55 (18.8)	67 (18.6)	76 (21.2)
≥ 60	23 (39.7)	22 (37.9)	82 (27.8)	73 (24.9)	241 (66.9)	239 (66.8)
VR_OSDI:						
Mean	1.0 (0.87)	1.2 (1.15)	0.9 (0.96)	0.9 (0.93)	1.4 (1.06)	1.5 (1.06)
Median	1.0	0.8	0.7	0.5	1.3	1.4
Range	0.0, 2.5	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0
Total OSDI:						
Mean	28.8 (16.50)	31.8 (21.31)	27.1 (18.15)	26.0 (19.04)	39.8 (20.43)	40.8 (21.84)
Median	29.6	27.3	22.7	20.8	39.6	37.5
Range	2.3, 60.4	2.8, 79.5	0.0, 75.0	0.0, 83.3	0.0, 93.8	0.0, 100.0
EDisS [2]:						
Mean	--	--	--	--	55.5 (24.93)	56.1 (25.39)
Median	--	--	--	--	56.5	56
Range	--	--	--	--	0.0, 100.0	0.0, 100.0
ODS:						
Mean	2.0 (1.17)	2.0 (1.04)	1.8 (1.16)	1.7 (1.19)	2.3 (1.08)	2.3 (1.03)
Median	2.0	2.0	2.0	2.0	3.0	2.0
Range	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0	0.0, 4.0

[1] EDS ≥ 40 at Days -14 and 0 was required in the OPUS-2 study; [2] Not collected in the Phase 2 and OPUS-1 studies
ICSS: Inferior corneal staining score; Total CSS: Total corneal staining score; Nasal CLGSS: Nasal conjunctival lissamine green staining score; STT: Schirmer Tear Test (mm/5 minutes); EDS: Eye Dryness Score (VAS); OSDI: Ocular Surface Disease Index; VR_OSDI: Vision related OSDI; EDisS: Eye Discomfort Score (VAS); ODS: Ocular Discomfort Score.

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Figure 6: Distribution of Baseline ICSS (ITT Population)

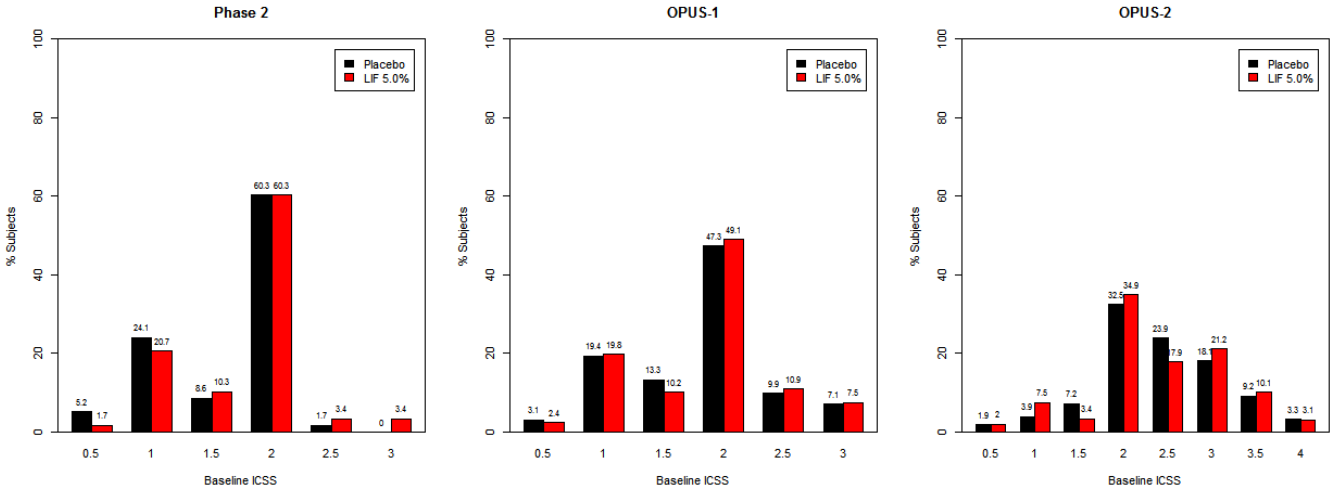


Figure 7: Distribution of Baseline Total CSS, Nasal CLGSS, and STT (ITT Population)

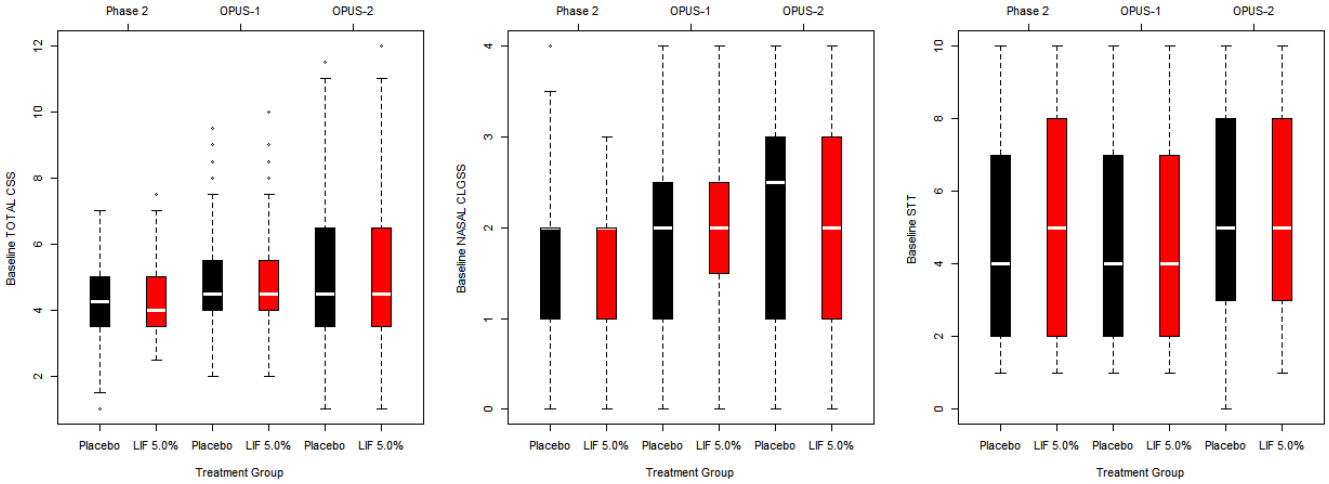
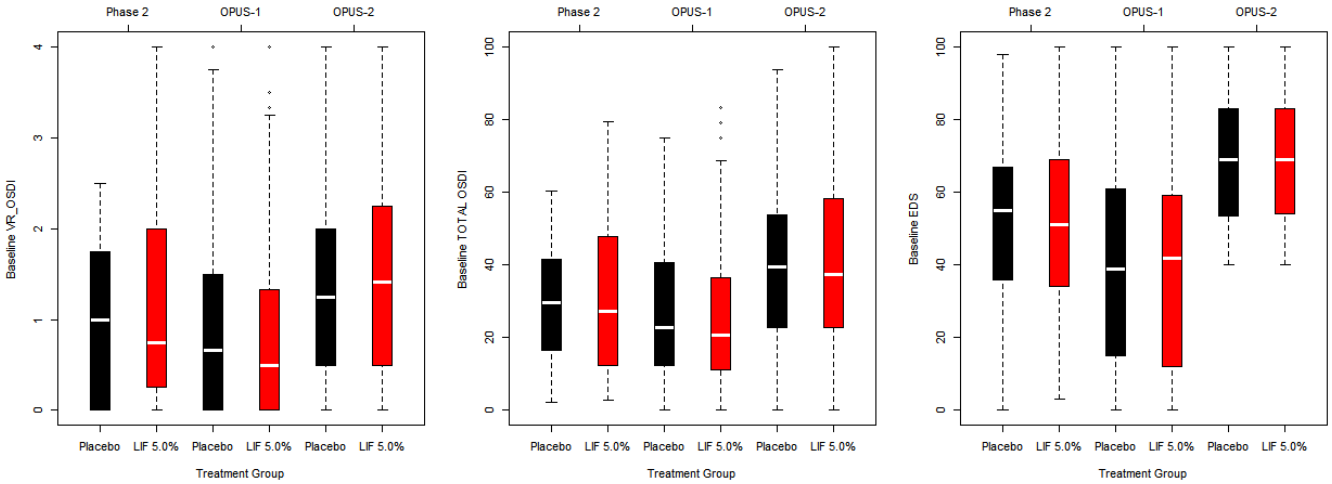


Figure 8: Distribution of Baseline VR_OSDI, Total OSDI, and EDS (ITT Population)



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3.2.4 Efficacy Results and Conclusions

The primary sign efficacy endpoint in each study was based on the inferior corneal staining score. The change from baseline in ICSS at Day 84 was the primary sign efficacy endpoint in OPUS-1 and OPUS-2 study while the actual ICSS at Day 84 was the primary sign efficacy endpoint in the Phase 2 study.

The change from baseline in VR_OSDI at Day 84 and the change from baseline in EDS at Day 84 were the co-primary symptom efficacy endpoints in OPUS-1 and OPUS-2 studies, respectively. There was no primary symptom efficacy endpoint defined in the Phase 2 study.

To compare LIF 5.0% ophthalmic solution againest Placebo in the sign and symptom endpoints, ANCOVA model was used in each study on the ITT population with LOCF for missing data. In the model, the change from baseline value at Day 84 was used as the response variable, and treatment, the baseline value, and the study specific strata (for OPUS-1 and OPUS-2) were used as covariates. Based on the model, the difference in the mean change between the treatment groups (LIF 5.0% minus Placebo) was determined using the least square means (LSM). The default observed margin (OM) option in the LSMEANS statement in SAS PROC MIXED was used to account for any imbalance in sample size and in the mean change values across strata.

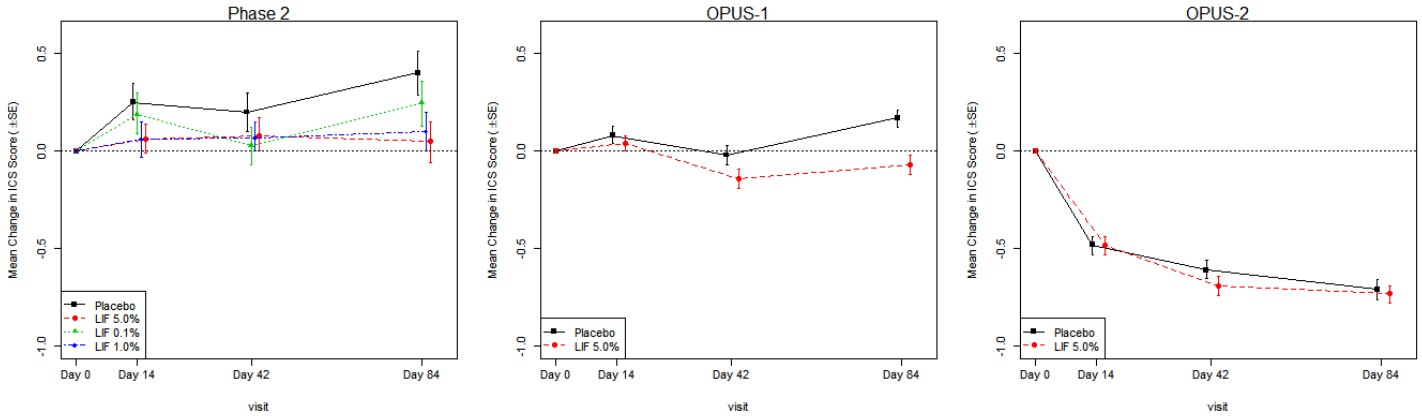
An unadjusted analysis based on a two sample t-test and a non-parametric Wilcoxon rank sum test was also performed in the three studies.

3.2.4.1 Co-Primary Endpoints

3.2.4.1.1 Primary Objective Endpoint: Inferior Corneal Staining Score (ICSS)

For each study, the mean changes in ICSS from baseline and standard errors (SE) at each visit were shown in Figure 9 below by treatment group.

Figure 9: Mean Change (±SE) in ICSS from Baseline at each Visit
(ITT Population, LOCF)



Source: Appendix Table 12; For the plot of the actual Mean in ICSS over time for each study, see Appendix Figure 32.

For the Phase 2 study, no reduction in ICSS was observed on average in the lifitegrast dose groups (LIF 0.1%, 1.0%, and 5.0%) as well as in the Placebo group throughout the study. However, a dose response in the mean change in ICSS was seen at Day 84. Since the greatest treatment effect was observed with LIF 5.0% dose group, the applicant studied this dose regimen

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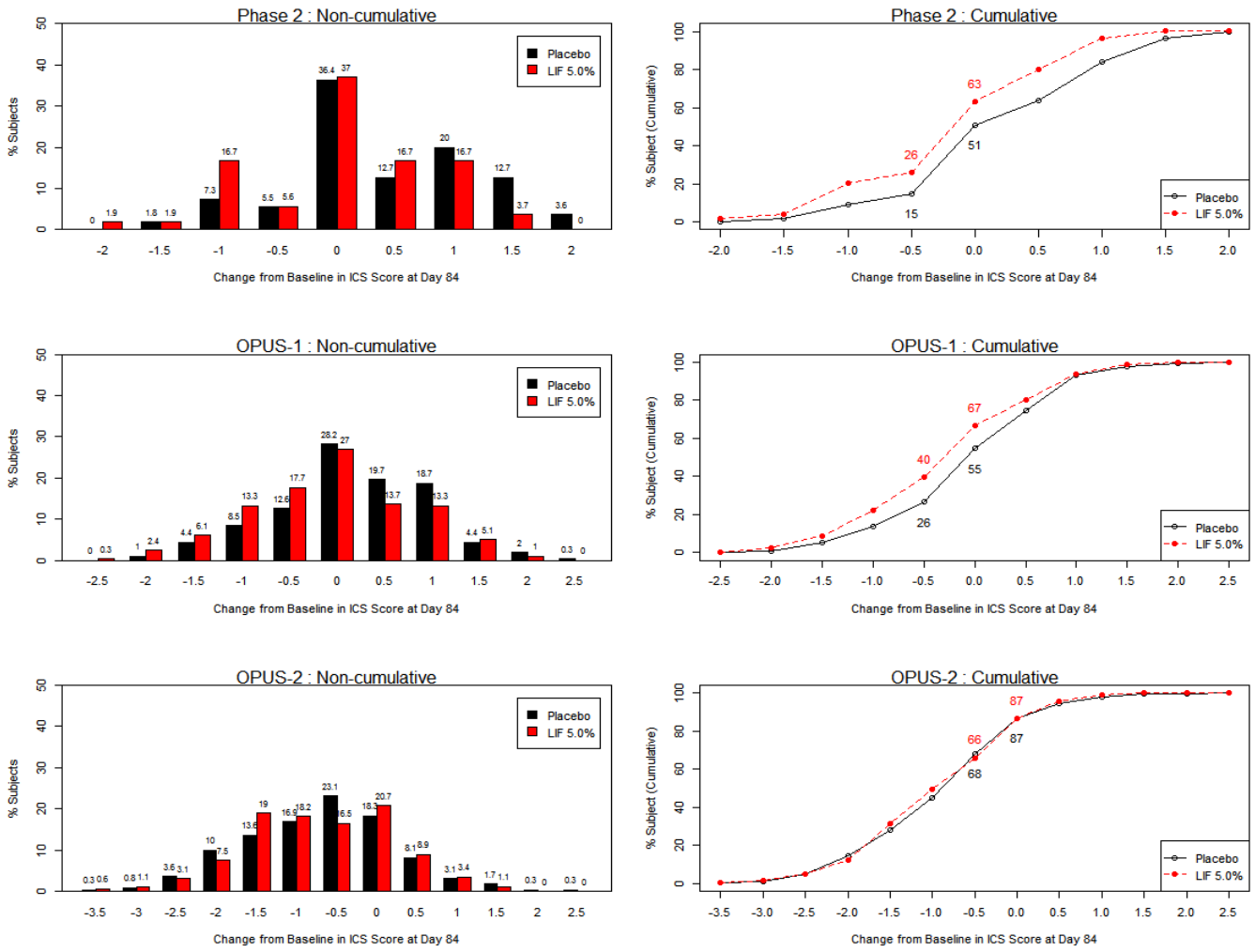
in the two Phase 3 studies. Therefore, for the phase 2 study in this review, only LIF 5.0% dose group was compared against Placebo with no multiplicity correction.

The mean changes in ICSS (±SE) from baseline at each visit for OPUS-1 and OPUS-2 studies were also shown in Figure 9. In OPUS-1 study, a clear separation in the mean change in ICSS was seen between the treatment groups as early as at Day 42, and it was maintained at the end of treatment period at Day 84 even though the magnitude of reduction observed at Day 42 was not maintained at Day 84 in both treatment groups.

In OPUS-2 study, both LIF 5.0% and Placebo group demonstrated larger mean reduction in ICSS compared with in the Phase 2 and OPUS-1 studies; in this study, the mean reductions between the treatment groups was comparable. Note that the Placebo group in OPUS-2 study, unlike in the Phase 2 and OPUS-1, demonstrated large mean reductions in ICSS throughout the treatment period. This was most likely due to the higher mean baseline score in OPUS-2 study than in the other studies (See Table 3); thus, in a more sever population with high baseline sign and symptom score, the Placebo solution which has a lubricant effect showed a considerable effect in improving clinical sign.

Figure 10: Distribution of change in ICSS from Baseline at Day 84
(ITT Population, LOCF)



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The distributions (both cumulative and non-cumulative) of the change in ICSS from baseline at Day 84 are shown in Figure 10 for all three studies.

In the Phase 2 and OPUS-1 studies, respectively, about 26% and 40% of LIF 5.0% treated subjects showed some form of reduction in ICSS compared with 15% and 26% of Placebo treated subjects. In the OPUS-2 study, a lot more subjects, about 66% of LIF 5.0% treated subjects and 68% of Placebo treated subjects, showed at least some form of reduction in ICSS at Day 84. In each treatment group, approximately 36% of subjects in the Phase 2 study, 27% of subjects in the OPUS-1 study, and 19% of subjects in the OPUS-2 study had no change in ICSS from baseline at Day 84. On the other hand, some form of worsening in ICSS from baseline at Day 84 was observed by 37%, 33%, and 13% of LIF 5.0% treated subjects compared with 49%, 45%, and 13% of placebo treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively.

In each study, the mean change in ICSS from baseline at Day 84 was compared between LIF 5.0% and Placebo treated groups using ANCOVA model. The summary of ICSS at baseline, Day 84, and the change from baseline at Day 84 based on the ITT population using the LOCF method are shown in Table 4.

Table 4: Mean Change in ICSS from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Summary	Placebo (N=58)	LIF 5.0% (N=58)	Placebo (N=294)	LIF 5.0% (N=293)	Placebo (N=360)	LIF 5.0% (N=358)
Baseline						
N	58	58	294	293	360	358
Mean (SD)	1.65 (0.513)	1.77 (0.515)	1.81 (0.599)	1.84 (0.597)	2.40 (0.722)	2.39 (0.763)
Median	2.00	2.00	2.00	2.00	2.50	2.50
(95% CI)	(1.51, 1.78)	(1.63, 1.90)	(1.75, 1.88)	(1.78, 1.91)	(2.33, 2.47)	(2.31, 2.47)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	2.05 (0.715)	1.83 (0.680)	1.98 (0.874)	1.77 (0.879)	1.69 (1.010)	1.66 (1.044)
Median	2.00	2.00	0.00	2.00	1.50	1.50
(95% CI)	(1.85, 2.24)	(1.65, 2.02)	(1.88, 2.08))	(1.67, 1.87)	(1.59, 1.80)	(1.55, 1.77)
Change from Baseline to Day 84						
Mean (SD)	0.40 (0.802)	0.05 (0.773)	0.17 (0.819)	-0.07 (0.868)	-0.71 (0.943)	-0.73 (0.926)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
95% CI	(0.18, 0.62)	(-0.16, 0.26)	(0.07, 0.26)	(-0.17, -0.04)	(-0.80, -0.61)	(-0.83, -0.64)
Based on adjusted analysis [1]:						
LS Means (SE)	0.35 (0.093)	0.10 (0.094)	0.16 (0.05)	-0.07 (0.05)	-0.7 (0.047)	-0.7 (0.05)
Diff.(minus Placebo) (95% CI)		-0.25 (-0.51, 0.02)		-0.23 (-0.36, -0.09)		-0.03 (-0.16, 0.10)
P-value: ANCOVA		0.0666		0.0007		0.6122
Based on unadjusted analysis:						
P-value: Student T-test		0.0209		0.0007		0.6562
P-value: Wilcoxon Test		0.0384		0.0006		0.7849

[1] Based on ANCOVA model that adjusted for the baseline ICS score in the phase 2 study and for the baseline and stratification factors in the OPUS-1 and OPUS-2 studies.

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In OPUS-1 study, LIF 5.0% treated group showed numerically larger mean reduction in ICSS from baseline at Day 84 compared with Placebo. The mean change in ICSS at Day 84 in the LIF 5.0% treated group was -0.07 (95% CI: -0.17, -0.04) and in the Placebo treated group was +0.17 (95% CI: 0.07, 0.26); the treatment difference (*LIF 5.0% minus Placebo*) was -0.23 (95% CI: -0.36, -0.09) and statistical significant difference was achieved in this study (p-value = 0.0007).

In the Phase 2 study, both LIF 5.0% and Placebo treated groups did not show mean reduction in ICSS from baseline throughout the study; however, a dose response in the mean change in ICSS was seen at Day 84 (See Figure 9). The mean change in ICSS at Day 84 in the LIF 5.0% treated group was +0.05 (95% CI: -0.16, 0.26) and in the Placebo treated group was +0.40 (95% CI: 0.18, 0.62); the treatment difference was -0.25 (95% CI: -0.51, 0.02) and not statistically significant (p-value = 0.0666). Though not statistically significant, the magnitude of treatment difference seen in this study (-0.25) was very close to what was seen in OPUS-1 study (-0.23); the non-statistical significant result in the Phase 2 study was likely due to smaller sample size compared with OPUS-1 study (note that the p-value in the Phase 2 study was close to 0.05).

In the OPUS-2 study, both treatment groups showed numerically larger mean reductions in ICSS throughout the study compared with in the Phase 2 and OPUS-1 studies. In this study, both treatment group demonstrated comparable mean reductions in ICSS at Day 84: the mean change in ICSS at Day 84 in the LIF 5.0% treated group was -0.73 (95% CI: -0.83, -0.64) and in the Placebo treated group was -0.71 (95% CI: -0.80, -0.61); the treatment difference was -0.03 (95% CI: -0.16, 0.10) and not statistically significant (p-value = 0.6122).

It should be noted that the larger mean reduction in ICSS observed in OPUS-2 study compared with in the Phase 2 and OPUS-1 studies was mainly due to the higher mean baseline score seen in OPUS-2 study than in the Phase 2 and OPUS-1 studies, and the lack of treatment difference in OPUS-2 study (in subjects with moderate-to-sever symptom) may be attributed to insufficient study duration. Note that the mean baseline ICSS in the Phase 2 and OPUS-1 studies and the mean ICSS at Day 84 in the OPUS-2 study (after treatment was received for 84 days) were comparable (See Table 4). Therefore, in order to see any separation between the treatment groups in OPUS-2 study that was seen in the Phase 2 and OPUS-1 studies, longer study duration may be needed.

In summary, statistical superiority in improving the clinical sign (as measured using ICSS) was demonstrated in only OPUS-1 study. In the Phase 2 and OPUS-2 studies, on the other hand, LIF 5.0% did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

The mean changes in ICSS from baseline at Days 14 and 42 were also compared between LIF 5.0% and Placebo group. The results are presented in Appendix Table 12.

3.2.4.1.2 Primary Subjective Endpoint in OPUS-1 Study: VR_OSDI Subscale Score

The change in VR_OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study and was supportive symptom endpoint in the Phase 2 and OPUS-2 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-2 studies were intended for descriptive use.

The efficacy results for the mean change in VR_OSDI score from baseline at each visit are shown in Figure 11 for each study.

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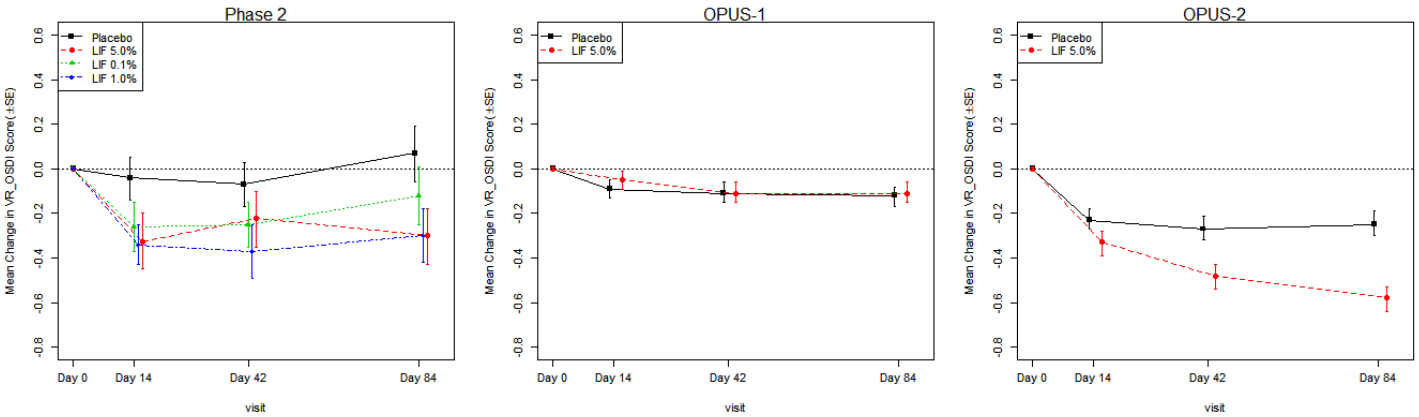
In the Phase 2 study, LIF 5.0% treated group demonstrated a relatively larger mean reductions in VR_OSDI score throughout the study compared with Placebo treated group; clear separations in the mean reductions in VR_OSDI score was seen between the treatment groups early on at Day 14 and then at the end of the study on Day 84. In the OPUS-1 study, both treatment groups demonstrated marginal reductions in VR_OSDI score from baseline throughout the study, and the rate of reductions was virtually the same between the treatment groups.

In the OPUS-2 study, both treatment groups demonstrated numerically larger mean reduction in VR_OSDI score from baseline throughout the study compared with in the Phase 2 and OPUS_1 studies; in this study, the mean reductions in the LIF 5.0% treated group was larger than in the Placebo treated group throughout the study.

Figure 11: Mean Change (± SE) in VR_OSDI from Baseline at each Visit



Source: Appendix Table 13. For the plot of the actual mean in VR_OSDI score over time for each study, see Appendix Figure 32.

The distributions of the change in VR_OSDI score from baseline at Day 84 (using kernel density estimations and cumulative distributions) are shown in Figure 12 for all three studies. In the OPUS-1 study, the distributions for the two treatment groups were virtually the same. In the Phase 2 and OPUS-2 studies, on the other hand, the distributions of the change in VR_OSDI score at Day 84 for LIF 5.0% treated subjects was shifted slightly towards the left compared with the distributions for Placebo treated subjects; that is, in these studies more LIF 5.0% treated subjects demonstrated some form of reductions and fewer LIF 5.0% treated subjects demonstrated some form of worsening compared with Placebo treated subjects.

Table 5: Proportion of Subjects with Mean Change in VR_OSDI at Day 84
(ITT Populaion, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Change	Placebo	LIF 5.0%	Placebo	LIF 5.0%	Placebo	LIF 5.0%
Change < 0	14 (25.4)	26 (48.2)	113 (38.3)	114 (39.0)	179 (49.9)	224 (62.8)
No Change (= 0)	16 (29.1)	12 (22.2)	85 (28.8)	89 (30.5)	66 (18.4)	59 (16.5)
Change > 0	25 (45.4)	16 (29.6)	97 (32.9)	89 (30.5)	114 (31.7)	74 (20.7)

The proportions of subjects with some form of reductions, with no change, or with some form of worsening in VR_OSDI score from baseline at Day 84 are shown in Table 5 and Figure 12 (cumulative distribution) for each study. For example, 23%, 1%, and 13% more LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed some form of reductions compared with Placebo treated subjects. On the other hand, 16%, 2%, and 11% fewer LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed

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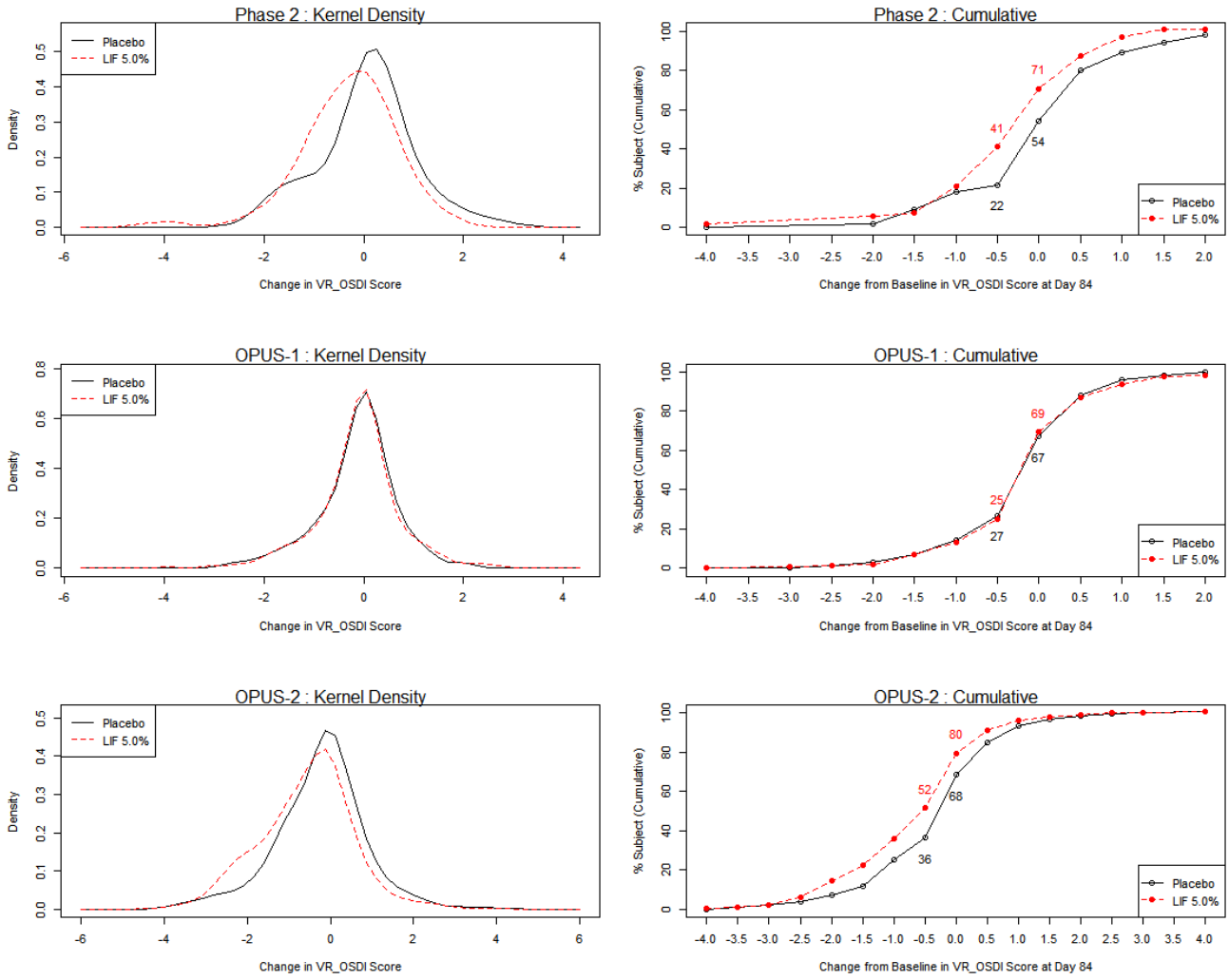
some form of worsening compared with Placebo treated subjects. Additionally, about the same percentage of subjects in each treatment group in OPUS-1 and OPUS-2 studies, and a slightly higher percentage of Placebo treated subjects in the Phase 2 study showed no change in VR_OSDI score from baseline at Day 84 (29% in Placebo versus 22% in LIF 5.0%).

Figure 12: Distribution of Change in VR_OSDI from Baseline at Day 84
(ITT Population, LOCF)



In each study, the mean change in VR_OSDI score from baseline at Day 84 was compared between LIF 5.0% and Placebo treated group using ANCOVA model. The summary of the VR_OSDI score at baseline, Day 84, and the change from baseline at Day 84 based on the ITT population using the LOCF method are shown in Table 6.

In the Phase 2 study, LIF 5.0% treated group showed numerically slightly larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group. The mean change in VR_OSDI score from baseline at Day 84 in the LIF 5.0% treated group was -0.30 (95% CI: -0.56, -0.05) and in the Placebo treated group was +0.07 (95% CI: -0.18, 0.32); the treatment difference was -0.30 (95% CI: -0.63, 0.03; p-value = 0.0712).

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In the OPUS-1 study, both treatment groups showed small and comparable mean reductions in VR_OSDI score from baseline throughout the study. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.11 (95% CI: -0.20, -0.01) and in the Placebo treated group was -0.12 (95% CI: -0.21, -0.04); the treatment difference was -0.01 (95% CI: -0.12, 0.10) and not statistically significant (p-value = 0.8261).

In OPUS-2 study, both treatment groups demonstrated larger mean reductions in VR_OSDI score from baseline throughout the study compared to in the Phase 2 and OPUS-1 studies. The mean change in VR_OSDI score at Day 84 in the LIF 5.0% treated group was -0.58 (95% CI: -0.70, -0.47) and in the Placebo treated group was -0.25 (95% CI: -0.36, -0.14); the treatment difference was -0.28 (95% CI: -0.41, -0.14; p-value < 0.0001).

Table 6: Mean Change in VR_OSDI from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	295	293	360	358
Mean (SD)	0.96 (0.865)	1.16 (1.148)	0.93 (0.958)	0.86 (0.931)	1.38 (1.065)	1.48 (1.062)
Median	1.00	0.75	0.67	0.50	1.25	1.42
(95% CI)	(0.74, 1.19)	(0.86, 1.46)	(0.82, 1.04)	(0.75, 0.96)	(1.27, 1.49)	(1.37, 1.59)
Day 84						
N	55	54	295	292	359	357
Mean (SD)	1.05 (1.173)	0.88 (0.961)	0.80 (0.838)	0.75 (0.861)	1.13 (1.047)	0.90 (0.998)
Median	0.67	0.67	0.50	0.50	1.00	0.50
(95% CI)	(0.74, 1.37)	(0.62, 1.14)	(0.71, 0.90)	(0.65, 0.85)	(1.03, 1.24)	(0.80, 1.01)
Change from Baseline to Day 84						
Mean (SD)	0.07 (0.929)	-0.30 (0.934)	-0.12 (0.762)	-0.11 (0.829)	-0.25 (1.069)	-0.58 (1.100)
Median	0.00	0.00	0.00	0.00	0.00	-0.50
(95% CI)	(-0.18, 0.32)	(-0.56, -0.05)	(-0.21, -0.04)	(-0.20, -0.01)	(-0.36, -0.14)	(-0.70, -0.47)
Based on adjusted analysis [1]:						
LS Means (SE)	0.03 (0.116)	-0.27 (0.117)	-0.11 (0.039)	-0.12 (0.039)	-0.28 (0.048)	-0.55 (0.048)
Diff.(minus Placebo) (95% CI)		-0.30 (-0.63, 0.03)		-0.01 (-0.12, 0.10)		-0.28 (-0.41, -0.14)
P-value: ANCOVA		0.0712		0.8261		<0.0001
Based on unadjusted analysis:						
P-value: Student T-test		0.0394		0.7860		<0.0001
P-value: Wilcoxon Test		0.0393		0.9063		<0.0001

[1] Based on ANCOVA model that adjusted for baseline VR_OSDI score in the phase 2 study and for the baseline VR_OSDI score and stratification factors in the OPUS-1 and OPUS-2 studies.

In summary, statistical superiority in improving the pre-defined clinical symptom endpoint (using VR_OSDI score) at Day 84 was not demonstrated in OPUS-1 study. In OPUS-2 study, LIF 5.0% treated subjects demonstrated a much larger improvement in VR_OSDI over Placebo and in the Phase 2 study showed a moderate improvement over Placebo. Additionally, a dose response improvement in VR_OSDI was seen at Day 84 (see Figure 11) in the Phase 2 study.

The mean changes in VR_OSDI score from baseline at Days 14 and 42 were also compared between LIF 5.0% and Placebo treated groups. The results are presented in Appendix Table 13.

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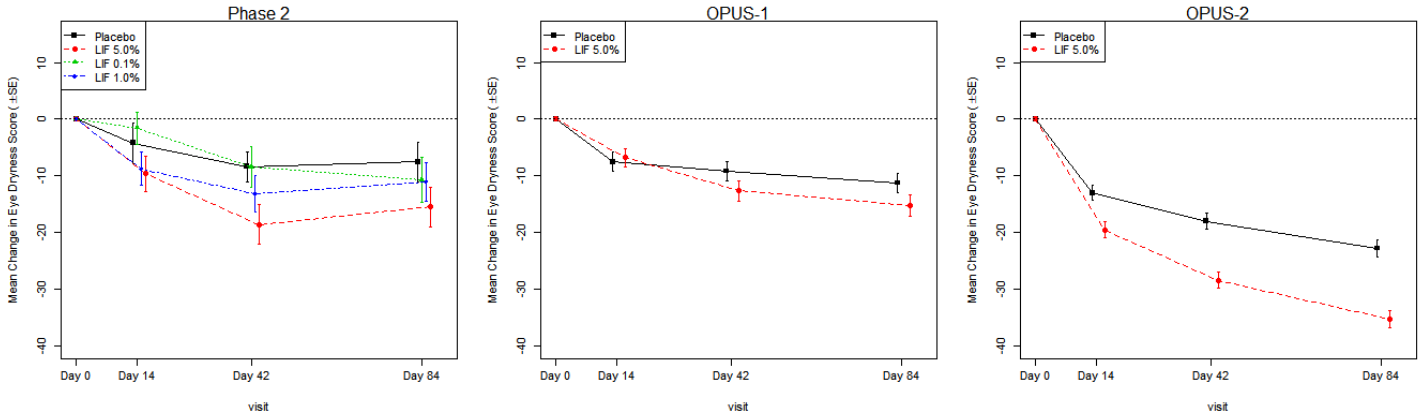
3.2.4.1.3 Primary Subjective Endpoint in OPUS-2 Study: Eye Dryness Score (EDS)

The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2 and was supportive symptom endpoint in the Phase 2 and OPUS-1 studies; thus, confidence intervals and p-values presented for the Phase 2 and OPUS-1 studies were intended for descriptive use.

The efficacy results for the mean change in EDS from baseline at each visit are shown in Figure 13 for each study. Within each study, both treatment groups demonstrated large mean reductions in EDS at each visit; however, the mean reductions in the LIF 5.0% treated group were numerically larger than in the Placebo treated group throughout the study. Clear separations between the treatment groups were seen early on at Day 14 in the Phase 2 and OPUS-2 studies and at Day 42 in the OPUS-1 study.

Figure 13: Mean Change (± SE) in EDS from Baseline at each Visit
(ITT Population, LOCF)



Source: Table 14; For the plot of the actual Mean in EDS over time for each study, see Appendix Figure 32.

The distributions of the change in EDS from baseline at Day 84 (using kernel density estimations and cumulative distributions) are shown in Figure 14 for all three studies.

The distributions of the change in EDS at Day 84 for LIF 5.0% treated group was slightly shifted to the left in the Phase 2 and OPUS-1 studies and more shifted to the left in the OPUS-2 study compared with placebo treated group; that is, more LIF 5.0% treated subjects demonstrated some form of reductions and fewer LIF 5.0% treated subjects demonstrated some form of worsening compared with Placebo treated subjects.

In Table 7 below, the proportions of subjects with some form of reduction, no change, or with some form of worsening are shown. For example, 10%, 5%, and 13% more LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed some form of reductions compared with Placebo treated subjects. On the other hand, 5%, 5%, and 12% fewer LIF 5.0% treated subjects in the Phase 2, OPUS-1, and OPUS-2 studies, respectively, showed some form of worsening compared with Placebo treated subjects. A small percentage of subjects in each treatment group of each study showed no change in EDS from baseline at Day 84.

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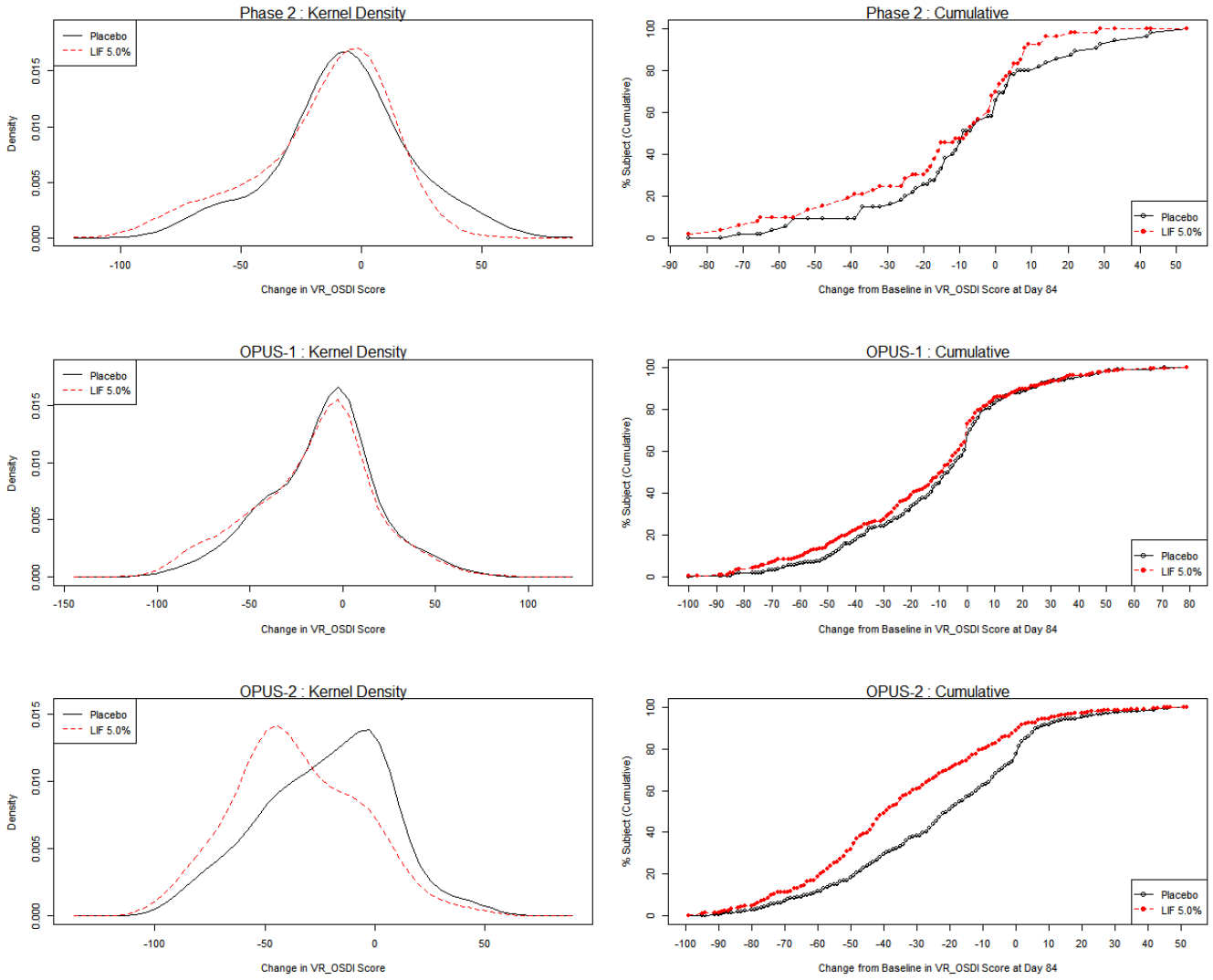
Table 7: Proportion of Subjects with Mean Change in EDS at Day 84
(ITT Population, LOCF)

	Phase 2		**OPUS-1**		**OPUS-2**	
Change	Placebo	LIF 5.0%	Placebo	LIF 5.0%	Placebo	LIF 5.0%
Change < 0	32 (58.2)	36 (67.9)	178 (60.4)	189 (64.5)	265 (73.6)	312 (87.1)
No Change (= 0)	4 (7.3)	1 (1.9)	24 (8.1)	25 (8.5)	14 (4.0)	6 (1.7)
Change > 0	19 (34.5)	16 (30.2)	93 (31.5)	79 (27.0)	81 (22.5)	40 (11.2)

Figure 14: Distribution of Change in EDS from Baseline at Day 84
(ITT Population, LOCF)



In each study, the mean change in EDS from baseline at Day 84 between LIF 5.0% and Placebo treated group were compared using ANCOVA model. The summary of EDS data at baseline, Day 84, and the change from baseline at Day 84 based on the ITT population using the LOCF method are shown in Table 8. Both treatment groups within each study displayed some form of improvement in EDS from baseline at Day 84.

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Table 8: Summary of Mean Change in EDS from Baseline at Day 84
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	57	295	293	360	358
Mean (SD)	51.81 (23.552)	51.58 (24.688)	41.62 (29.690)	40.18 (28.645)	69.22 (16.761)	69.68 (16.954)
Median	55.00	51.00	39.00	42.00	69.00	69.00
(95% CI)	(45.62, 58.00)	(45.03, 58.13)	(38.22, 45.02)	(36.88, 43.47)	(67.48, 70.95)	(67.92, 71.44)
Day 84						
N	55	54	295	293	360	358
Mean (SD)	44.11 (27.130)	37.06 (27.578)	30.39 (30.773)	25.00 (28.870)	46.47 (29.875)	34.39 (27.862)
Median	47.00	35.00	19.00	11.00	50.00	28.00
(95% CI)	(36.77, 51.44)	(29.53, 44.58)	(26.86, 33.91)	(21.68, 28.32)	(43.37, 49.56)	(31.49, 37.28)
Change from Baseline to Day 84						
N	55	53	295	293	360	358
Mean (SD)	-7.55 (25.929)	-15.49 (25.987)	-11.23 (28.783)	-15.17 (31.482)	-22.75 (28.600)	-35.30 (28.400)
Median	-9.00	-7.00	-6.00	-9.00	-20.00	-39.00
(95% CI)	(-14.55, -0.54)	(-22.65, -8.33)	(-14.53, -7.94)	(-18.79, -11.55)	(-25.71, -19.79)	(-38.25, -32.34)
Based on adjusted analysis [1]:						
LS Means (SE)	-7.70 (3.240)	-15.3 (3.301)	-10.9 (1.530)	-15.5 (1.536)	-22.9 (1.450)	-35.2 (1.454)
Diff.(minus Placebo) (95% CI)		-7.63 (-16.8, 1.54)		-4.68 (-8.94, -0.43)		-12.3 (-16.4, -8.30)
P-value: ANCOVA		0.1021		0.0311		<0.0001
Based on un-adjusted analysis:						
P-value: Student T-test		0.1148		0.1137		<0.0001
P-value: Wilcoxon Test		0.2890		0.1376		<0.0001

[1] Based on ANCOVA model that adjusted for baseline EDS in the phase 2 study and for baseline EDS and stratification factors in the OPUS-1 and OPUS-2 studies.

LIF 5.0% treated subjects in the Phase 2 study showed numerically better improvement in EDS over Placebo. In this study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.5 (95% CI: -22.6, -8.3) and in the Placebo treated group was -7.6 (95% CI: -14.6, -0.5); the treatment difference was -7.6 (95% CI: -16.8, 1.5; p-value = 0.1021). Note that the confidence interval for the treatment difference did not exclude zero, and this was likely due to the smaller sample size.

LIF 5.0% treated subjects in the OPUS-1 study also showed numerically better improvement in EDS over Placebo. In this study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -15.2 (95% CI: -18.8, -11.6) and in the Placebo treated group was -11.2 (95% CI: -14.5, -7.9); the treatment difference was -4.7 (95% CI: -8.9, -0.4; p-value = 0.0311).

In this study, a much larger improvement in EDS from baseline at Day 84 was seen in a small subgroup of subjects with a recent history of ATU and with baseline EDS ≥40 (N = 67 in Placebo and N = 63 in LIF 5.0%). In this subgroup (see Figure 15 and Appendix Table 21), the mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.4 (95% CI: -43.4, -27.4) and in the Placebo treated group was -22.1 (95% CI: -29.8, -14.4); the treatment difference was -15.3 (95% CI: -25.9, -4.7).

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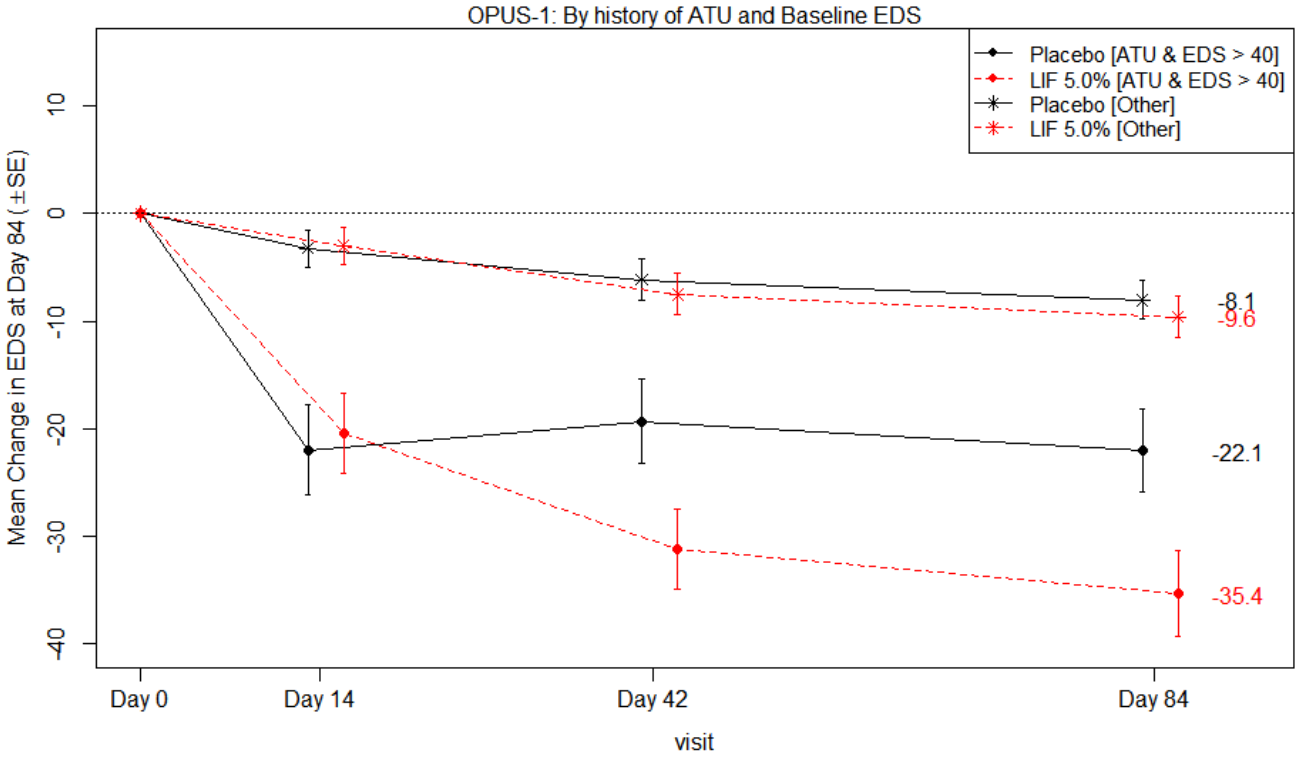
Note that the considerable improvement in EDS seen in the subgroup of subjects in the OPUS-1 study led to the design of OPUS-2 study, and as such, the OPUS-2 study enrolled subjects with a recent history of ATU and with baseline EDS ≥ 40, and used EDS as a co-primary symptom endpoint in the study.

Therefore, as was seen in the subgroup of patients in the OPUS-1 study, both treatment groups in the OPUS-2 study demonstrated large mean reduction in EDS throughout the study; and the mean reduction at Day 84 in the LIF 5.0% treated group was higher than in the Placebo treated group by about 12 units. In this study, the mean change in EDS at Day 84 in the LIF 5.0% treated group was -35.3 (95% CI: -38.3, -32.3) and in the Placebo treated group was -22.8 (95% CI: -25.7, -19.8); the treatment difference was -12.3 (95% CI: -16.4, -8.3) and was strongly statistically significant (p-value < 0.0001).

Figure 15: Mean Change (± SE) in EDS by History of ATU and Baseline EDS in OPUS-1 (ITT Population, LOCF)



Source: Appendix Table 21

In summary, both treatment groups within each study demonstrated large mean reductions in EDS from baseline throughout the study; statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated in OPUS-2 study. Both the Phase 2 and OPUS-1 studies showed numerically better improvement in EDS in the LIF 5.0% treated subjects over Placebo. Additionally, a dose response improvement in EDS was seen at Day 84 (see Figure 13) in the Phase 2 study.

In each study, the mean changes in EDS at Days 14 and 42 were also compared between the LIF 5.0% and Placebo treated groups. The results are presented in Appendix Table 14.

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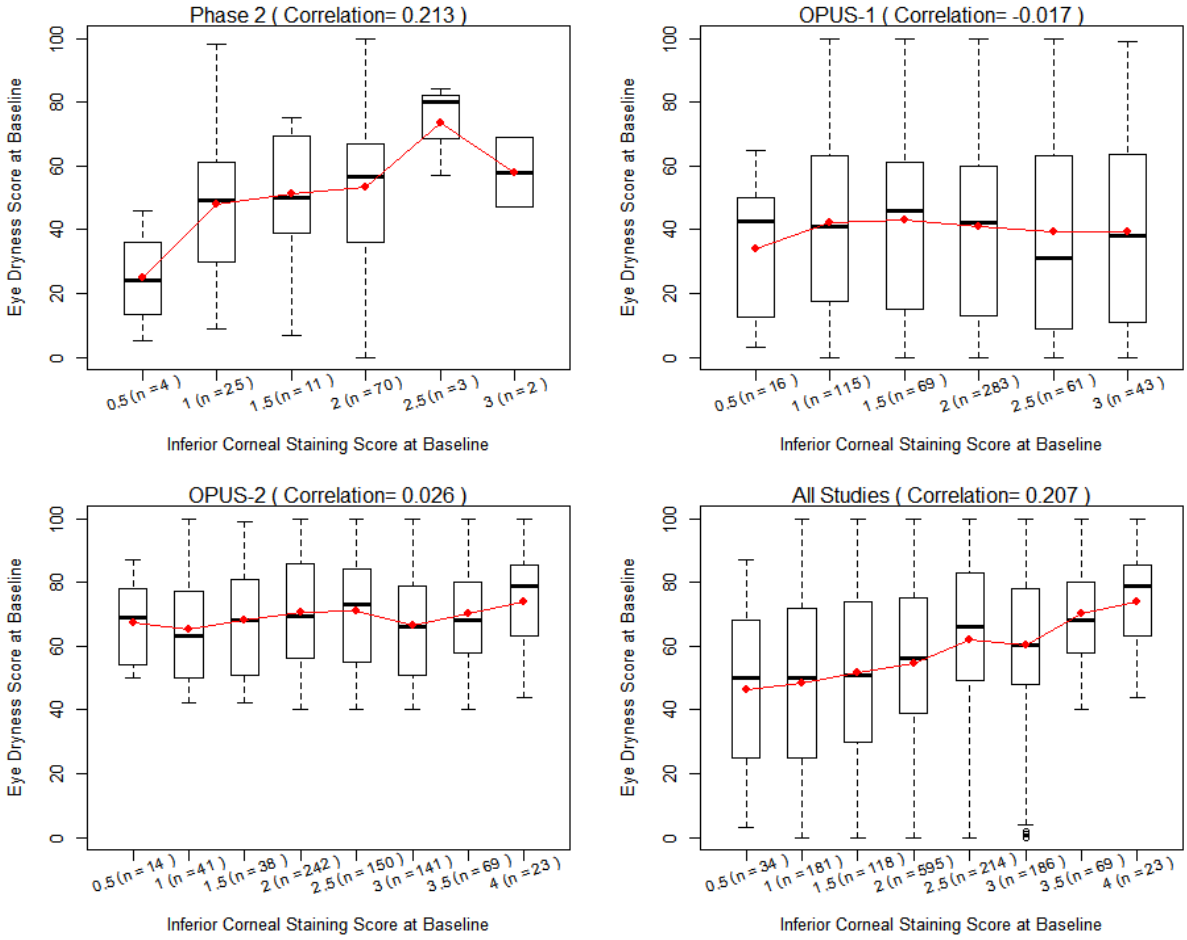
3.2.4.2 Relationship between the Co-primary Efficacy Endpoints

In this NDA application, superiority of LIF 5.0% over Placebo in improving clinical sign or clinical symptom of dry eye was not demonstrated in two or more studies; significant improvement in ICSS was demonstrated in OPUS-1 study while significant improvement in EDS and in VR_OSDI was demonstrated in OPUS-2 study. To study the association between the sign and symptom of dry eye, we examined the relationship between ICSS and EDS at baseline (before treatment was received) and at Day 84 (after treatment was received for 84 days) using data from the two Phase 3 and Phase 2 studies.

Baseline ICSS by Baseline EDS

The plots of baseline ICSS by baseline EDS based on data from each individual study and from the pooled study are shown in Figure 16. In the OPUS-1 and OPUS-2 studies, no apparent relationship was seen between ICSS and EDS at baseline; however; a slight increase in EDS with an increase in ICSS (correlation = 0.21) was seen based on the Phase 2 and the pooled data.

Figure 16: Relationship between ICSS and EDS at Baseline
(ITT Population)



ICSS AT Day 84 by EDS at Day 84

The plots of ICSS at Day 84 by EDS at Day 84 are shown in Figure 17 by treatment group for each study. A slight increase in EDS with an increase in ICSS was seen in LIF 5.0% treated group in the OPUS-1 study (correlation = 0.19) and in Placebo treated group in the OPUS-2

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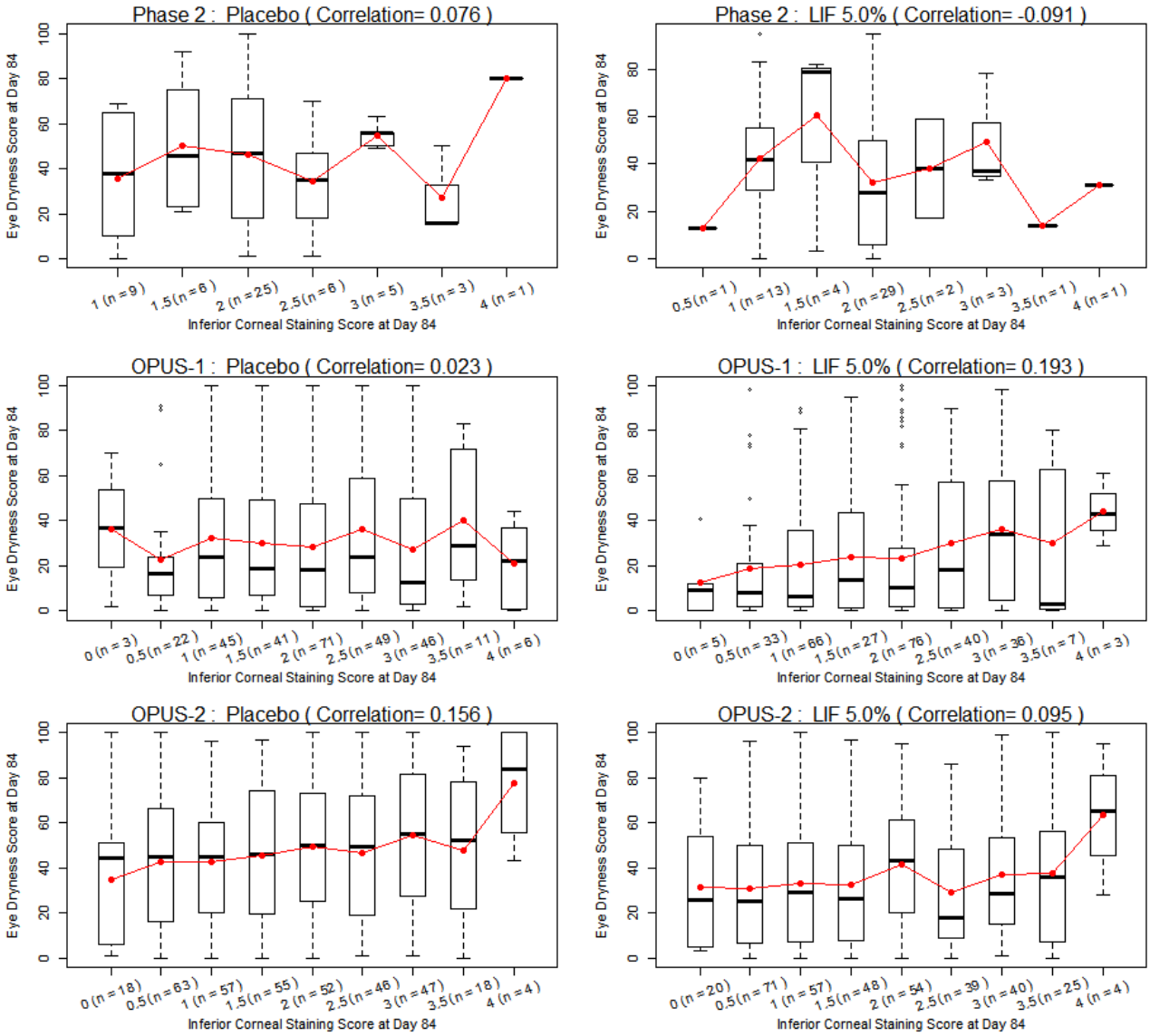
study (correlation = 0.16). However, no apparent relationship was seen between ICSS and EDS data at Day 84 in both treatment groups in the Phase 2 study, in the Placebo treated group in the OPUS-1 study, and in the LIF 5.0% treated group in the OPUS-2 study.

Figure 17: Relationship between ICSS and EDS at Day 84
(ITT Population)



Meanc change in ICSS, EDS, and VR_OSDI by baseline ICSS category

Furthermore, the mean changes in ICSS, EDS, and VR_OSDI score from baseline at Day 84 were summarized by baseline ICSS category (< 2.0, = 2.0, 2.0 – 3.0, and >3.0); the results based on OPUS-1 and OPUS-2 are shown in Figure 18. Note that since the maximum baseline ICSS in the OPUS-1 was <=3.0 by design, the > 3.0 category was applicable for only OPUS-2 study.

From the first raw in Figure 18, we observe that subjects with baseline ICSS < 2.0 in both studies did not show improvement in ICSS at Day 84; however, subjects with baseline ICSS ≥2.0 in LIF 5.0% treated group in both studies and in Placebo treated group in OPUS-2 study showed large improvement in ICSS at Day 84.

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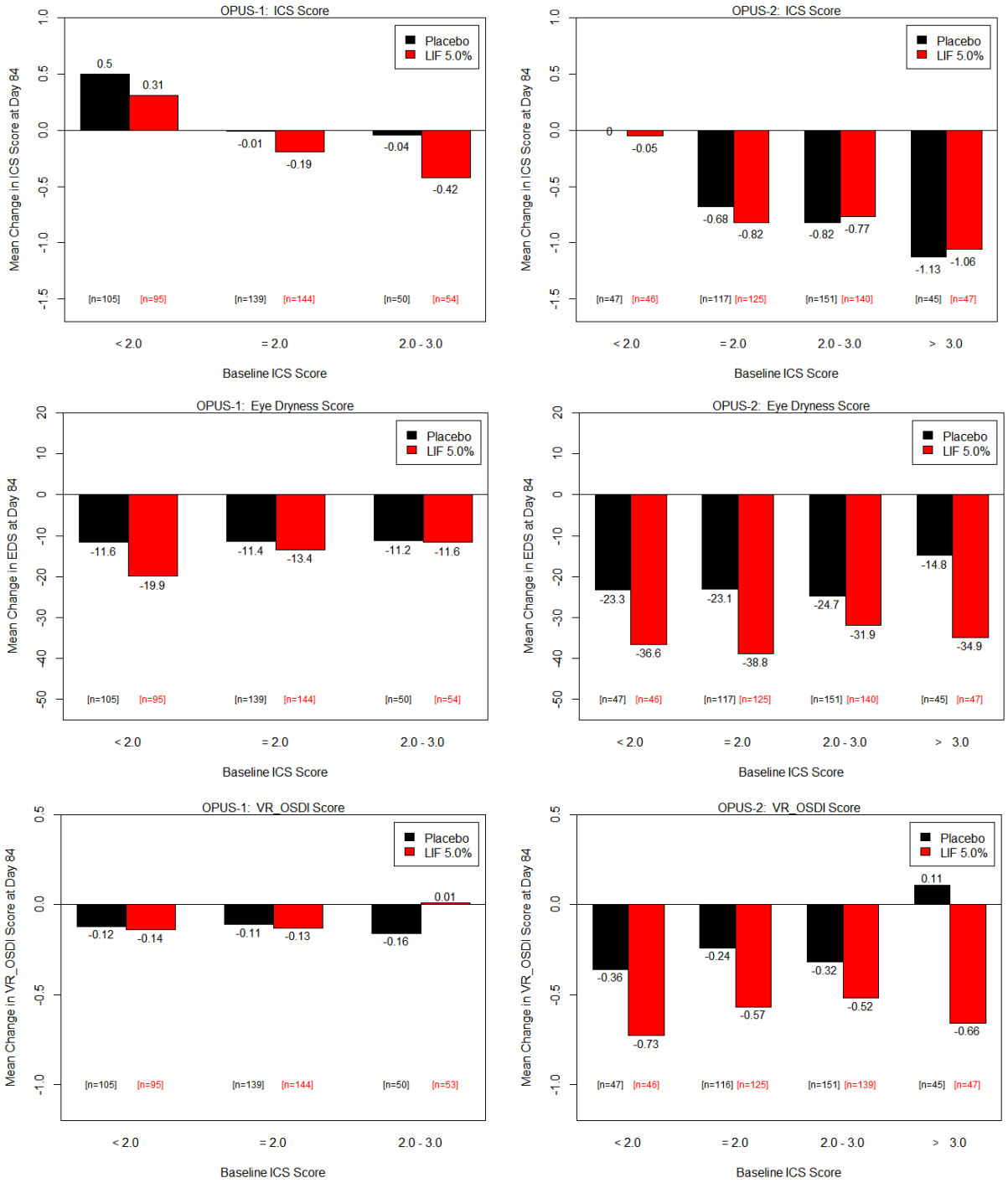
Figure 18: Mean Change in ICS, EDS, and VR_OSDI at Day 84 by Baseline ICS Category (ITT Population, LOCF)



In both studies, large mean reductions in EDS at Day 84 were observed within each of the baseline ICSS categories (see 2nd row of Figure 18); in the Placebo treated group, the mean reductions observed in each of the baseline ICSS categories were about the same in both studies whereas in LIF 5.0% treated group, subjects with baseline ICS score of ≤ 2.0 had a slightly larger mean reductions in EDS compared with subjects with baseline ICS score of > 2.0. The results for

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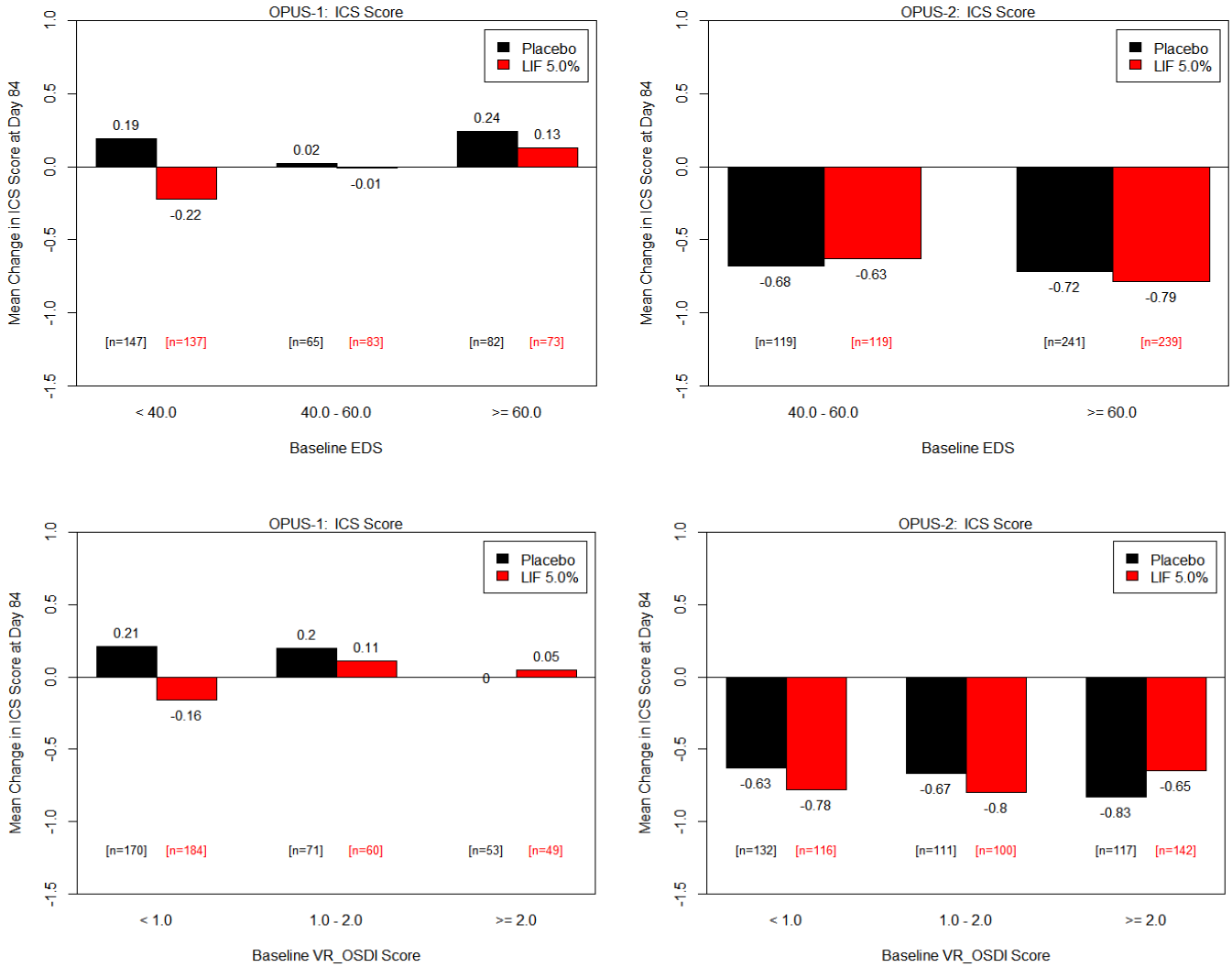
the mean reductions in VR_OSDI score at Day 84 (See Figure 18 3rd row) by baseline ICSS categories were similar to what was seen for the mean reduction in EDS.

Meanc change in ICSS by baseline EDS and VR_OSDI category

In Figure 19, the mean changes in ICSS from baseline at Day 84 were summarized by baseline EDS score category (<40.0, 40.0 - 60.0, and >= 60.0) and by baseline VR_OSDI score category (< 1.0, 1.0 - 2.0, and >= 2.0). Note that since the baseline EDS in the OPUS-2 study was ≥ 40.0 by design, the < 40.0 category is applicable only for OPUS-1 study.

Figure 19: Mean Change in ICSS at Day 84 by Baseline EDS and VR_OSDI Score Category (ITT Population, LOCF)



In subjects with baseline EDS 40 – 60 and ≥ 60 categories, both Placebo and LIF 5.0% treated groups in the OPOS-2 study demonstrated large and numerically comparable mean reductions in ICS score at Day 84 while both treatement groups in the OPUS-1 study did not show mean reductions in these categories. In subjects with baseline EDS < 40.0 in the OPUS-1 study, only LIF 5.0% treated subjects demonstrated mean reductions in ICSS at Day 84. The pattern for the mean reduction in ICSS at Day 84 by the baseline VR_OSDI categories was similar to the pattern seen by the baseline EDS cateogries.

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In summary, when the mean reductions in ICSS at Day 84 was summarized by the baseline EDS and VR_OSDI categories, clear and consistent pattern was not seen between OPUS-1 and OPUS-2 study.

Meanc change in ICSS by baseline EDS and ICSS category

The mean reduction in ICSS at Day 84 was further summarized by the combination of baseline ICSS (< 2.0, =2.0, 2.0–3.0, and >3.0) and baseline EDS (<40.0, 40.0 - 60.0, and >= 60.0) categories. The results for OPUS-1 and OPUS-2 studies are shown in Figure 20 and Figure 21.

Figure 20: Mean Change in ICSS from Baseline at Day 84 by Baseline ICSS and EDS (OPUS-1) (ITT Population, LOCF)

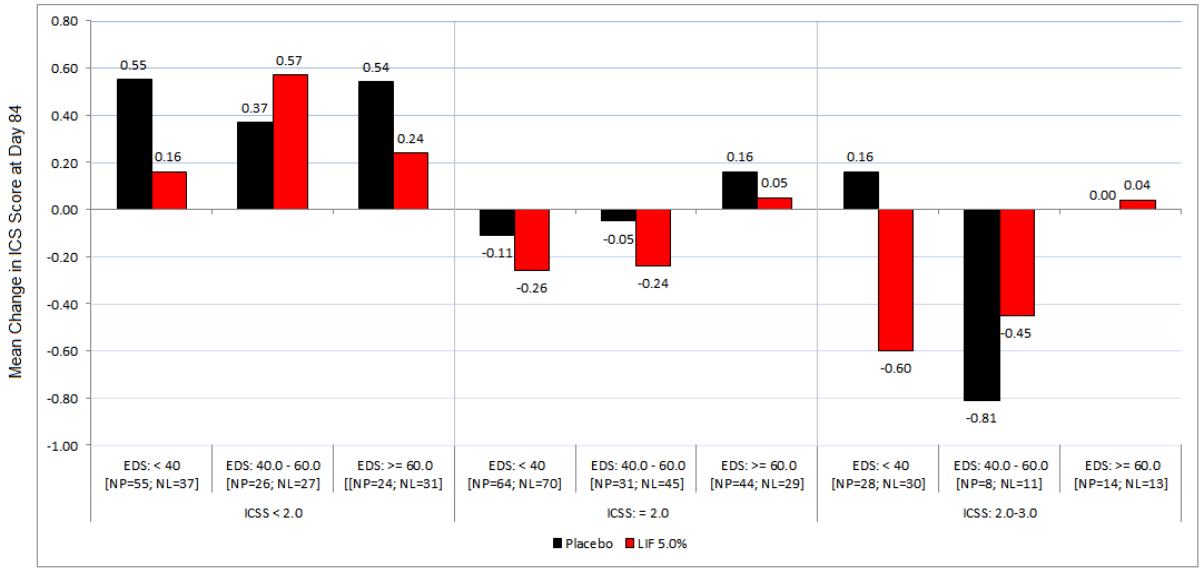
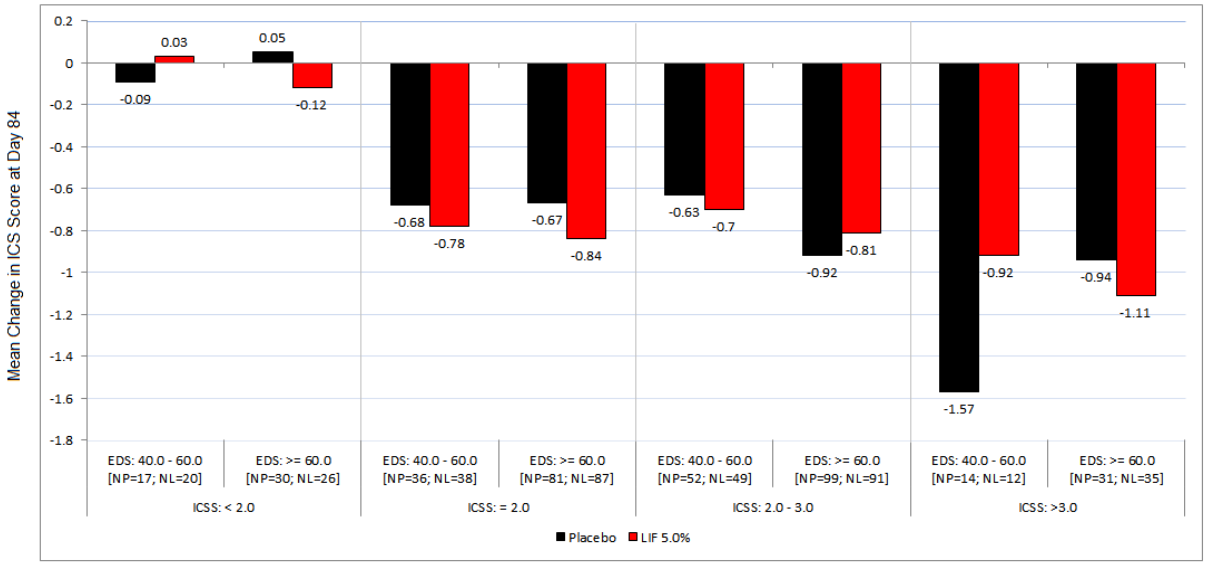


Figure 21: Mean Change in ICSS from Baseline at Day 84 by Baseline ICSS and EDS (OPUS-2) (ITT Population, LOCF)



In summary, when the mean reductions in ICSS at Day 84 was summarized by the combination of baseline ICSS and baseline EDS categories, clear and consistent pattern was not seen in OPUS-1 and OPUS-2 study.

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3.2.4.3 Secondary Efficacy Endpoints

In each study protocols, several sign and symptom secondary efficacy endpoints were defined. All the secondary efficacy variables in each study and at each time point were analyzed using the same analysis method used for the co-primary efficacy endpoints.

In the Phase 2 study, all the secondary efficacy endpoints were intended to be exploratory in nature, and hence no formal correction for multiplicity was performed across the secondary endpoints. In the OPUS-1 and OPUS-2 studies, a testing strategy was defined in the study protocols to control the Type I error rates across the secondary endpoints if both co-primary endpoints were significant. However, statistical significance was not achieved in the symptom co-primary endpoint in the OPUS-1 study and in the sign co-primary endpoint in the OPUS-2 study. Therefore, treatment comparisons for all secondary endpoints presented for these studies were considered as descriptive; that is, confidence intervals and p-values were presented as descriptive statistics without multiplicity correction.

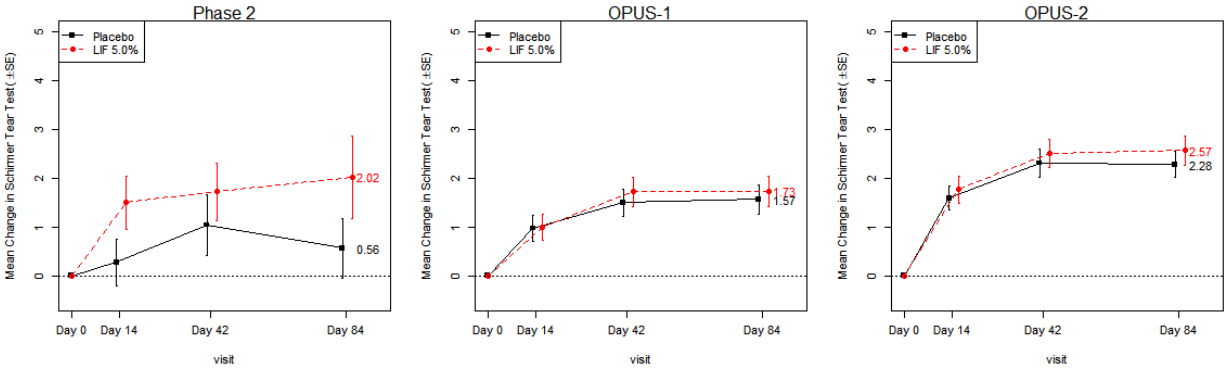
3.2.4.3.1 Mean Change in the Schirmer Tear Test (STT) Score - Sign

The schirmer tear test (without anesthesia) - an objective (sign) efficacy endpoint - measured tear production based on the length of wetting area (in mm/5 minutes). The mean STT score was defined in the Phase 2 and OPUS-1 studies as the secondary sign endpoint.

To evaluate the effectiveness of each treatment group in improving tear production, the length of wetting area was compared between the treatment groups - longer wetting area was associated with better efficacy benefit.

The mean STT score at baseline was about 5 mm in each study; the mean baseline score was balanced between the treatment groups. For each study, the mean changes in STT score from baseline at each visit are shown in Figure 22 for each study.

Figure 22: Mean Change in STT (in mm/5 minutes) Score from Baseline
(ITT Population, LOCF)



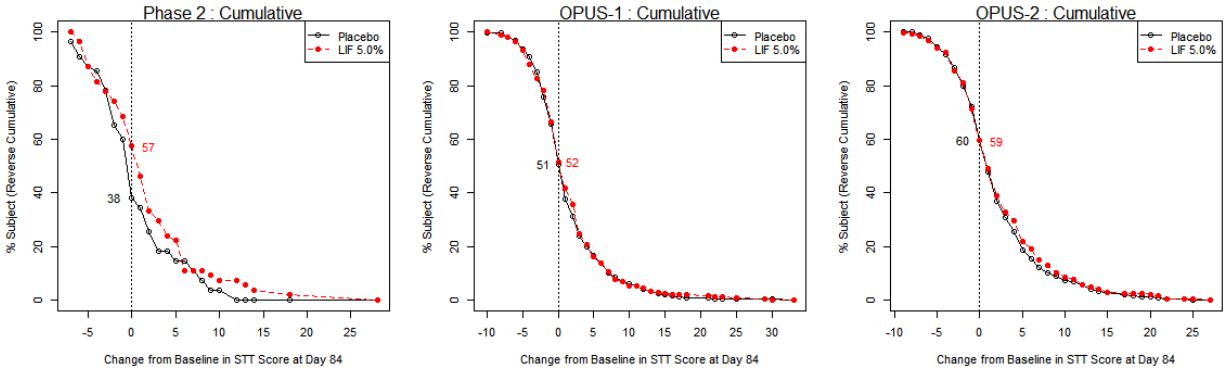
Source: Appendix Table 15

In the Phase 2 study, LIF 5.0% treated group had a larger mean increase in STT score throughout the study compared with Placebo treated group. In the OPUS-1 and OPUS-2 studies, both Placebo and LIF 5.0% treated group demonstrated large mean increase in STT score from baseline throughout the study. The mean increases at Days 42 and 84 were slightly higher in the LIF 5.0% treated group; however, a statistical significance difference was not achieved at any of the time points in all the studies (See Appendix Table 15).

Reference ID: 3795926

In Figure 23 below, the revers cumulative distribution for the change in STT score from baseline at Day 84 are shown. In the OPUS-1 and OPUS-2 studies, the distributions for the Placebo and LIF 5.0% treated group were indistinguishable; about 50% of subjects in each treatment group in the OPUS-1 study and about 60% of subjects in each treatment group in the OPUS-2 study showed some form of increase in STT score from baseline at Day 84. In the Phase 2 study, on the other hand, about 20% more LIF 5.0% treated subjects showed some form of increase in STT score at Day 84 compared with Placebo treated subjects.

Figure 23: Cumulative Distribution of Change in STT Score from Baseline at Day 84
(ITT Population, LOCF)



3.2.4.3.2 Mean Change in Total Corneal Staining Score (Total CSS) - Sign

Objective assessment for dry eye was also assessed using the total corneal staining scores (Total CSS). The mean change in Total CSS from baseline at Day 84 was defined in the OPUS-2 study as the secondary sign endpoint.

The Total CSS included the three regions of corneal fluorescein staining (inferior, central, and superior) where each region was scored in 0-4 scale with 0.5 increment (0 = no staining); the Total CSS was derived as the sum of the three regions (0-12 points). Note that the inferior corneal staining score (ICSS) was the primary efficacy sign endpoint in each study.

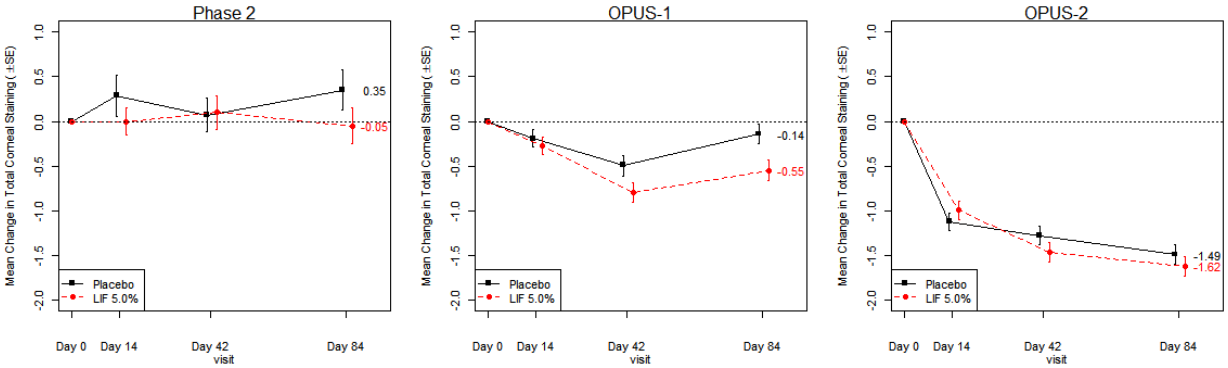
The mean Total CSS at baseline was about 4.3 in the Phase 2 study, about 4.8 in OPUS-1 study, and about 5.2 in the OPUS-2 study. The mean changes (± SE) in Total CSS from baseline at each visit are shown in Figure 24 for each study. The overall pattern for the mean change in Total CSS score over time was closely similar to the pattern observed for the mean change in ICSS over time (See Figure 9).

In each study, LIF 5.0% treated group had numerically larger mean reduction in the Total CSS at Day 84 compared with Placebo treated group; however, statistical significance difference in the mean change in Total CSS between the treatment groups was achieved in only OPUS-1 study (See Appendix Table 16).

Both treatment groups in the OPUS-2 study demonstrated larger mean reductions in Total CSS from baseline throughout the study compared with in the Phase 2 and OPUS-1 studies; however, in this study, the mean reductions between the treatment groups at Day 84 were virtually the same.

Reference ID: 3795926

Figure 24: Mean Change in Total CSS from Baseline over Time
(ITT Population, LOCF)



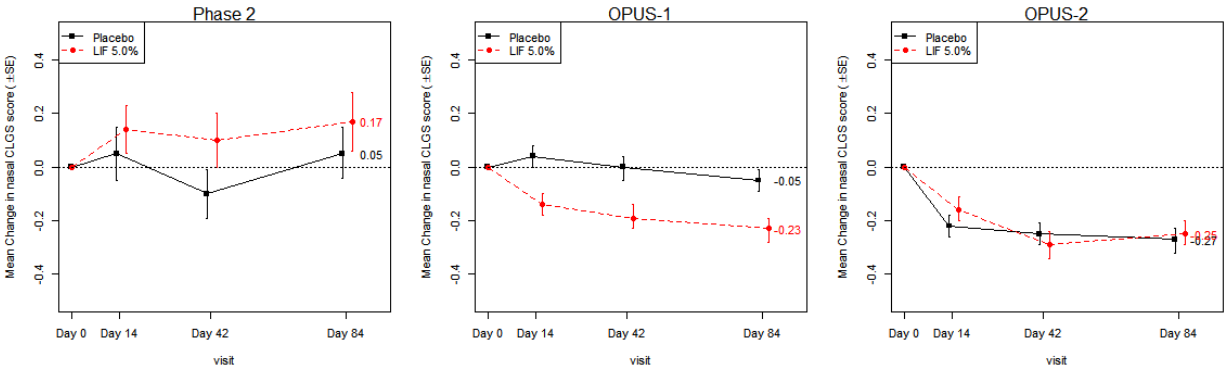
Source: Appendix Table 16

3.2.4.3.3 Mean Change in Nasal Conjunctival Lissamine Green Staining Score (Nasal CLGSS) – Sign

Objective assessment for dry eye was also assessed using Nasal CLGSS. The mean change in Nasal CLGSS from baseline at Day 84 was defined in the OPUS-2 study as the secondary sign endpoint. Similar to the corneal fluorescein staining, conjunctival lissamine green staining were also scored in 0-4 scale with 0.5 increment (0 = no staining).

The mean Nasal CLGSS at baseline was about 1.7 in the Phase 2 study, about 1.9 in OPUS-1 study, and about 2.1 in the OPUS-2 study. The mean changes (± SE) in Nasal CLGSS from baseline at each visit are shown in Figure 25 for each study.

Figure 25: Mean Change in Nasal CLGS Score from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 17

In the Phase 2 study, LIF 5.0% appeared to be less effective than Placebo in improving Nasal CLGSS; however, this may be due to slight difference in the baseline score; note that in this study, 10% more subjects in the Placebo group had baseline score > 1.5 compared with LIF 5.0%. In the OPUS-1 study, LIF 5.0% treated group appeared to be more effective in improving Nasal CLGSS throughout the study, and at each visit, statistical significant difference in the mean reduction in Nasal CLGSS was achieved between the treatment groups (See Appendix Table 17). The baseline scores in this study as well were slightly unbalanced; about 10% more subjects in the LIF 5.0% group had baseline score > 1.5 compared with in the Placebo group.

Reference ID: 3795926

In OPUS-2, both Placebo and LIF 5.0% groups demonstrated large and comparable mean reductions in Nasal CLGSS from baseline throughout the study. However, in this study, statistical significant difference was not achieved between the treatment groups at each visit.

3.2.4.3.4 Mean Change in Total OSDI Score – Symptom

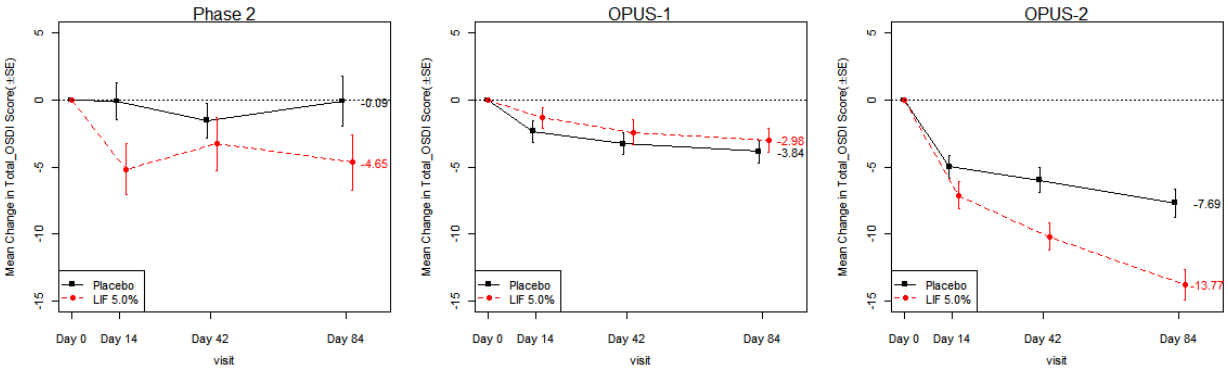
Subjective assessment for dry eye was evaluated using Total OSDI score at each visit. The mean change in Total OSDI score from baseline at Days 42 and 84 was defined in the OPUS-1 study as the secondary symptom endpoint.

The OSDI measured in 0-100 scale (0=normal, 100=sever) was derived from 12 items subject-reported questionnaire with data at each visit collected retrospectively with a 1-week recall period across both eyes. Each of the 12 items was graded in a 0-4 scale and the total score was converted to 0-100 scale. Note that the visual related OSDI subscale (VR_OSDI) was the co-primary symptom endpoint in the OPUS-1 study.

In the Phase 2 study, the mean baseline Total OSDI score in LIF 5.0% group was higher than in Placebo group by 3 units; in OPUS-1, the median baseline score in Placebo group was higher than LIF 5.0% by 2 units; the mean baseline scores in OPUS-2 study were comparable.

The mean changes (± SE) in the Total OSDI score from baseline at each visit are shown in Figure 26 by treatment group for each study. The efficacy benefit in improving Total OSDI score from baseline at each visit was compared between the treatment groups.

Figure 26: Mean Change in Total OSDI Score from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 18

In the Phase 2 study, LIF 5.0% treated group had numerically larger mean reductions in the Total OSDI score throughout the study compared with Placebo.

In the OPUS-1 study, Placebo treated group showed numerically slightly better improvement in the Total OSDI score throughout the study; however, the difference in the mean reductions between the treatment groups was very small. Note that the Placebo group in this study had slightly higher baseline score and the numerical advantage may be attributed to that.

In the OPUS-2 study, both treatment groups showed large mean reductions in Total OSDI score from baseline throughout the study; however, the mean reductions in the LIF 5.0% treated group were numerically larger than in the Placebo treated group by about 4 units at Days 42 and by about 6 units at Day 84 (See Appendix Table 18).

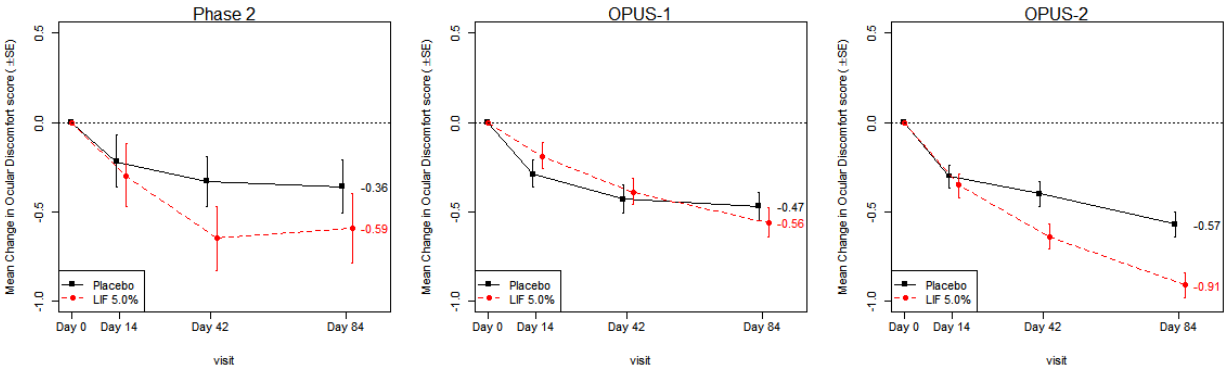
Reference ID: 3795926

3.2.4.3.5 Mean Change in Ocular Discomfort Score (ODS) – Symptom

Subjective assessment for dry eye was also assessed using ocular discomfort score (ODS) at each visit; ODS was measured in 0–4 point scale (0=no discomfort; 4= constant discomfort). The mean change in ODS from baseline at Day 84 was defined in the OPUS-2 study as the secondary symptom endpoint.

Within each study, the mean ODS at baseline was comparable between the treatment groups; the mean baseline ODS was about 2.0 in the Phase 2 study, 1.7 in OPUS-1 study, and 2.3 in the OPUS-2 study. The mean changes (± SE) in ODS from baseline at each visit are shown in Figure 27 for each study.

Figure 27: Mean Change in ODS from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 19

In all three studies, both Placebo and LIF 5.0% treated group demonstrated mean reductions in ODS from baseline throughout the study.

In the Phase 2 and OPUS-2 studies, LIF 5.0% treated group had numerically larger mean reductions in ODS compared with Placebo treated group throughout the study; however, the Placebo treated group in OPUS-1 study had numerically slightly higher mean reductions early on while the LIF 5.0% treated group showed numerically slightly higher mean reduction at Day 84 (See Appendix Table 19).

3.2.4.3.6 Mean Change in Eye Discomfort Score (EDisS) – Symptom

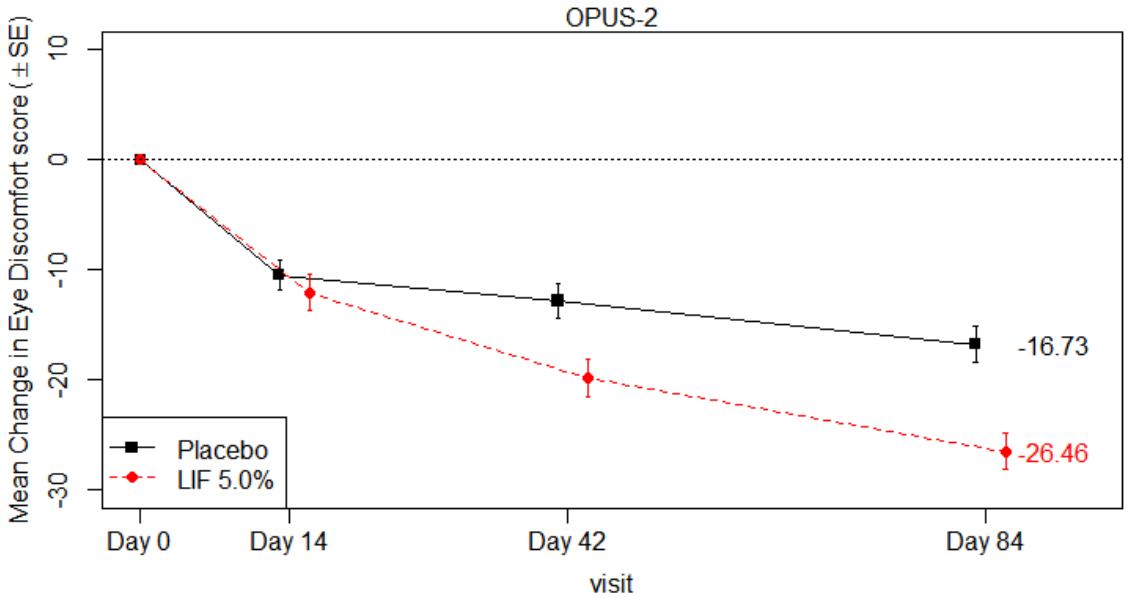
Subjective assessment for dry eye was also assessed using the eye discomfort score (EDisS) of the 7-item VAS at each study visits in OPUS-2 study only; EDisS was measured in 0-100 point scale (0 = no discomfort; 100=maximum discomfort) across both eyes.

The mean EDisS at baseline was about 55 units in each treatment group. The mean changes (± SE) in EDisS from baseline at each visit are shown in Figure 28 by treatment group for each study.

Clearly, both treatment groups demonstrated large mean reductions in EDisS from baseline throughout the study; however, LIF 5.0% treated group demonstrated numerically higher mean reductions throughout the study compared with Placebo treated group. At Day 84, the mean reduction in EDisS was higher in the LIF 5.0% treated group by about 9 units (p-value < 0.0001) (See Appendix Table 20).

Reference ID: 3795926

Figure 28: Mean Change in Total ODS Score from Baseline over Time
(ITT Population, LOCF)



Source: Appendix Table 20

3.2.4.4 Exploratory Efficacy Endpoints

In each study, a number of exploratory sign and symptom efficacy endpoints were defined in the study specific protocols. The efficacy results for these endpoints were presented and discussed in the applicant clinical study summary reports. For the results of these exploratory endpoints, we defer to the clinical study report.

3.2.4.5 Sensitivity Analysis

In the Phase 2, OPUS-1, and OPUS-2 study, respectively, a total of 20 (17%), 23 (4%), and 49 (14%) subjects discontinued before Week 12. The discontinuation rate in each treatment group in the Phase 2 study (about 10% each) and in OPUS-1 study (about 4% each) was comparable. In the OPUS-2 study, on the other hand, the discontinuation rate in the LIF 5.0 treated group was three times higher than in the Placebo treated group (10% in the LIF 5.0% treated group versus 3% in the Placebo treated group). In all studies, the most common reason for discontinuation in the LIF 5.0% treated groups was due to adverse events.

To assess the impact on the primary analyses result of missing data due to drop-outs and to assess the robustness of the primary sign and symptom efficacy results under different data handling approaches, several sensitivity analyses were performed:

- ANCOVA analysis using observed data (without missing data imputation) and using worst observation carried forward (WOCF) for imputing missing data, and
- A mixed model repeated measure analysis (MMRM) using observed data.

The results for the primary sign and symptom efficacy endpoints and for the key secondary sign and symptom endpoints at Day 84 based on these analyses methods are shown in Appendix Table 22, Table 23, and Table 24. The results from the sensitivity analyses methods were consistent with the primary efficacy analysis approach that used LOCF method for imputing missing data .

Reference ID: 3795926

3.3 Safety evaluation

In this section a high level safety summary for the individual Phase 2, OPUS-1, OPUS-2, and SONATA study, and for the integrated safety population was provided; a comprehensive safety evaluation of the product is primarily covered in the FDA clinical review. The Phase 2, OPUS-1, and OPUS-2 studies were designed to evaluate the safety and efficacy of LIF 5.0% compared to Placebo whereas the SONATA study was specifically designed to evaluate the safety of LIF 5.0% compared to Placebo in subjects with dry eye.

The SONATA study was a Phase 3, multicenter, randomized, double–masked and placebo–controlled study. The key inclusion criteria in this study were similar to in the OPUS-2 study. In this study, a total of 332 subjects were randomized to either LIF 5.0% or Placebo (2:1) and received treatment twice daily for one year (360 days) to compare the safety profiles. In this study, a total 19 (17%) Placebo treated subjects and 50 (23%) LIF 5.0% treated subjects discontinued before one year. Adverse event (AE) was the most common reason for discontinuation in both treatment groups (about 12% in LIF 5.0% versus 8% in Placebo).

In all studies, safety was evaluated based on all randomized subjects who received at least a single dose of double blind treatment. The high level safety summary in this review included extent of exposure to study drug and adverse events (AEs).

The integrated safety population included a total of 1753 subjects; 823 subjects were included in the placebo treated group and 930 subjects were included in the LIF 5.0% treated group. Subjects included in the integrated safety population had mean age of 60 years at enrollment, most subjects were white (87%), and there were more women (76%) than men.

3.3.1 Exposure to Study Drug

The summary of exposure to study drug are shown in Table 9 below. In each study, the mean duration of exposure to study drug was numerically slightly lower in the LIF 5.0% treated group compared to the Placebo treated group whereas the median duration of exposure was comparable between the treatment groups.

Table 9: Summary of Duration of Exposure to Study Drug
(Safety Analysis Population)

	Placebo				LIF 5.0%			
Studies	N	Mean (SD)	Median	Range	N	Mean (sd)	Median	Range
Phase 2 [1]	58	80.5 (14.3)	84	13 - 95	58	75.2 (21.7)	84	14 - 91
OPUS-1 [2]	295	84.0 (7.8)	85	21 - 132	293	82.3 (11.0)	85	13 - 92
OPUS-2 [3]	359	82.1 (8.8)	85	14 - 94	359	78.2 (17.8)	85	1 - 93
SONATA [4]	111	311.3 (114.3)	359	1 - 370	220	304.4 (112.5)	359	1 - 377

Source - Clinical Study Reports: [1] Table 14.3.11; [2] Table 4.1.2; [3] Table 4.1.1; [4] Table 4.1.1

3.3.2 Adverse Events

In the combined studies, a total of 1753 subjects (823 in Placebo and 930 in LIF 5.0%) were exposed to study drug. The high level summary of treatment emergent AEs (TEAEs) by treatment group are shown in Table 10 for the individual study data and for the pooled data.

Reference ID: 3795926

In all studies, a higher percentage of LIF 5.0% treated subjects reported at least one TEAE compared to Placebo treated subjects. In the integrated population, at least 25% more LIF 5.0% treated subjects reported at least one TEAE compared with Placebo treated subjects. The incidences of TEAEs considered by the investigator as drug-related were also significantly higher in the LIF 5.0% treated group than in the Placebo treated group (16% in Placebo versus 49% in LIF 5.0% in the integrated population).

Table 10: Overview of Treatment Emergent Adverse Events by Treatment Group
(Safety Analysis Population)

	Phase 2		**OPUS-1**		**OPUS-2**		**SONATA**		**Pooled**	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 359)**	**LIF 5.0% (N = 359)**	**Placebo (N = 111)**	**LIF 5.0% (N = 220)**	**Placebo (N = 823)**	**LIF 5.0% (N = 930)**
Subjects with at least 1 TEAE	30 (51.7)	48 (82.8)	125 (42.4)	210 (71.7)	92 (25.6)	172 (47.9)	59 (53.2)	160 (72.7)	306 (37.2)	590 (63.4)
Ocular TEAEs	15 (25.9)	40 (69.0)	75 (25.4)	174 (59.4)	59 (16.4)	121 (33.7)	38 (34.2)	118 (53.6)	187 (22.7)	453 (48.7)
Non-ocular TEAEs	22 (37.9)	19 (32.8)	77 (26.1)	106 (36.2)	45 (12.5)	96 (26.7)	40 (36.0)	104 (47.3)	184 (22.4)	325 (35.0)
Subjects with moderate or severe TEAEs	15 (27.6)	14 (27.6)	41 (13.9)	51 (17.4)	26 (8.0))	69 (22.2)	28 (27.9)	71 (37.2)	110 (13.4)	205 (22.0)
Ocular TEAEs	1 (1.7)	8 (13.8)	8 (2.7)	21 (7.2)	12 (3.3)	37 (10.3)	11 (9.9)	33 (15.0)	32 (3.9)	99 (10.6)
Non-ocular TEAEs	15 (25.9)	8 (13.8)	34 (11.5)	30 (10.2)	17 (4.7)	43 (11.9)	20 (18.0)	49 (22.2)	86 (10.4)	130 (14.0)
Subjects with treatment-related TEAEs	14 (24.1)	39 (67.2)	51 (17.3)	172 (58.7)	41 (11.4)	142 (39.6)	27 (24.3)	104 (47.3)	133 (16.2)	457 (49.1)
Ocular TEAEs	13(22.4)	38 (65.5)	49 (16.6)	161 (54.9)	37 (10.3)	102 (28.4)	23 (20.7)	88 (40.0)	122 (14.8)	389 (41.8)
Non-ocular TEAEs	2 (3.5)	7 (12.1)	6 (2.0)	47 (16.0)	6 (1.7)	70 (19.5)	6 (5.4)	41 (18.6)	20 (2.4)	165 (17.7)
Subjects prematurely withdrawn due to TEAEs	5 (8.6)	6 (10.3)	3 (1.0)	8 (2.7)	3 (0.8)	26 (7.2)	10 (9.0)	27 (12.3)	21 (2.6)	67 (7.2)
Ocular TEAEs	2 (3.4)	6 (10.3)	2 (0.7)	6 (2.1)	2 (0.6)	23 (6.4)	6 (5.4)	18 (8.2)	12 (1.5)	53 (5.7)
Non-ocular TEAEs	3 (5.2)	0 (0.0)	1 (0.7)	2 (0.3)	1 (0.3)	6 (1.7)	4 (3.6	9 (4.1)	9 (1.1)	17 (1.8)
Subjects with serious TEAEs	1 (1.7)	0 (0.0)	2 (0.7)	5 (1.7)	4 (1.1)	3 (0.8)	6 (5.4)	9 (4.1)	13 (1.6)	17 (1.8)
Ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular TEAEs	1 (1.7)	0 (0.0)	2 (0.7)	5 (1.7)	4 (1.1)	3 (0.8)	6 (5.4)	9 (4.1)	13 (1.6)	17 (1.8)
Subjects with TEAEs resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)
Ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)

The summary of ocular TEAEs occurring in ≥1% of subjects in either treatment group based on the pooled study are presented in Table 11. The overall incidence of ocular TEAE was significantly larger in the LIF 5.0% treated group than in the Placebo treated

group (23% in Placebo versus 49% in LIF 5.0% in the integrated population). The most frequent ocular TEAE in the LIF 5.0% treated group were instillation site irritation (16% versus 3% in Placebo), instillation site pain (11% versus 2% in Placebo) and instillation site reaction (12% versus 1% in Placebo).

Table 11: Ocular TEAEs Occurring in ≥1% of Subjects in either Treatment Group in the Pooled Study (Integrated Analysis; SAF)

	Phase 2		**OPUS-1**		**OPUS-2**		**SONATA**		**Pooled**	
	Placebo (N = 58)	**LIF 5.0% (N = 58)**	**Placebo (N = 295)**	**LIF 5.0% (N = 293)**	**Placebo (N = 359)**	**LIF 5.0% (N = 359)**	**Placebo (N = 111)**	**LIF 5.0% (N = 220)**	**Placebo (N = 823)**	**LIF 5.0% (N = 930)**
Subjects with at least 1 Ocular TEAE	**15 (25.9%)**	**40 (69.0%)**	**75 (25.4%)**	**174 (59.4%)**	**59 (16.4%)**	**121 (33.7)**	**38 (34.2%)**	**118 (53.6)**	**187 (22.7%)**	**453 (48.7%)**
Eye Disorders	**9 (15.5%)**	**10 (17.2%)**	**47 15.9%)**	**55 (18.8%)**	**47 (13.1%)**	**85 (23.7%)**	**33 (29.7%)**	**82 (37.3%)**	**136 (16.5%)**	**232 (24.9%)**
Visual Acuity Reduced	3 (5.2%)	1 (1.7%)	15 (5.1%)	14 (4.8%)	23 (6.4%)	18 (5.0%)	7 (6.4%)	25 (11.4%)	48 (5.8%)	58 (6.2%)
Vision Blurred	1 (1.7%)	0 (0.0%)	3 (1.0%)	3 (1.0%)	2 (0.6%)	10 (2.8%)	4 (3.6%)	9 (4.1%)	10 (1.2%)	22 (2.4%)
Lacrimation Increased	0 (0.0%)	2 (3.4%)	1 (0.3%)	7 (2.4%)	1 (0.3%)	9 (2.5%)	2 (1.8%)	8 (3.6%)	4 (0.5%)	26 (2.8%)
Eye Irritation	0 (0.0%)	0 (0.0%)	3 (1.0%)	4 (1.4%)	1 (0.3%)	11 (3.1%)	1 (0.9%)	8 (3.6%)	5 (0.6%)	23 (2.5%)
Eye Pruritus	1 (1.7%)	0 (0.0%)	2 (0.7%)	5 (1.7%)	4 (1.1%)	4 (1.1%)	2 (1.8%)	8 (3.6%)	9 (1.1%)	17 (1.8%)
Eye Pain	0 (0.0%)	1 (1.7%)	5 (1.7%)	6 (2.0%)	1 (0.3%)	5 (1.4%)	0 (0.0%)	7 (3.2%)	6 (0.7%)	19 (2.0%)
Ocular Hyperaemia	0 (0.0%)	2 (3.4%)	4 (1.4%)	7 (2.4%)	2 (0.6%)	4 (1.1%)	0 (0.0%)	4 (1.8%)	6 (0.7%)	17 (1.8%)
Conjunctival Hyperaemia	1 (1.7%)	0 (0.0%)	1 (0.3%)	1 (0.3%)	4 (1.1%)	5 (1.4%)	4 (3.6%)	6 (2.7%)	10 (1.2%)	12 (1.3%)
Dry Eye	1 (1.7%)	1 (1.7%)	2 (0.7%)	0 (0.0%)	2 (0.6%)	2 (0.6%)	6 (5.5%)	4 (1.8%)	11 (1.3%)	7 (0.8%)
Conjunctival Haemorrhage	0 (0.0%)	3 (5.2%)	2 (0.7%)	2 (0.7%)	1 (0.3%)	4 (1.1%)	1 (0.9%)	1 (0.5%)	4 (0.5%)	10 (1.1%)
General Disorders And Administration Site Conditions	**9 (15.5%)**	**37 (63.8%)**	**28 (9.5%))**	**142 (48.5%)**	**11 (3.1%)**	**57 (15.9%)**	**7 (6.3%)**	**51 (23.2%)**	**55 (6.7%)**	**287 (30.9%)**
Instillation Site Irritation	6 (10.3%)	20 (34.5%)	12 (4.1%)	69 (23.5%)	5 (1.4%)	28 (7.8%)	5 (4.5%)	33 (15.0%)	28 (3.4%)	150 (16.1%)
Instillation Site Pain	3 (5.2%)	20 (34.5%)	11 (3.7%)	63 (21.5%)	3 (0.8%)	11 (3.1%)	2 (1.8%)	7 (3.2%)	19 (2.3%)	101 (10.9%)
Instillation Site Reaction	0 (0.0%)	8 (13.8%)	2 (0.7%)	50 (17.1%)	4 (1.1%)	25 (7.0%)	2 (1.8%)	29 (13.2%)	8 (1.0%)	112 (12.0%)
Instillation Site Pruritus	0 (0.0%)	2 (3.4%)	6 (2.0%)	19 (6.5%)	0 (0.0%)	8 (2.2%)	1 (0.9%)	5 (2.3%)	7 (0.9%)	34 (3.7%)
Instillation Site Lacrimation	0 (0.0%)	1 (1.7%)	1 (0.3%)	7 (2.4%)	0 (0.0%)	1 (0.3%)	1 (0.9%)	3 (1.4%)	2 (0.2%)	12 (1.3%)
Instillation Site Foreign Body Sensation	0 (0.0%)	2 (3.4%)	2 (0.7%)	0 (0.0%)	0 (0.0%)	3 (0.8%)	0 (0.0%)	6 (2.7%)	2 (0.2%)	11 (1.2%)

Reviewer Analysis

Reference ID: 3795926

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

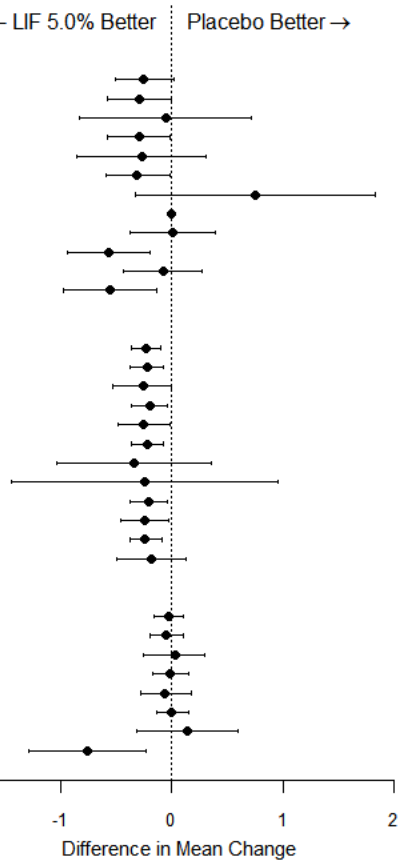
In each study, the co-primary clinical sign and symptom efficacy endpoints were analyzed by the subgroup of age, sex, race, and history of ATU using the primary efficacy analysis approach. Note that all subjects in OPUS-2 study had a history of artificial tear use (ATU).

Using ANCOVA analysis: the least square mean estimates (SE) for each treatment group, and the treatment differences (dots) with 95% confidence interval estimates (horizontal bars) by the subgroups are shown in Figure 29 for the mean change in ICSS, in Figure 30 for the mean change in VR_OSDI score, and in Figure 31 for the mean change in EDS.

The co-primary efficacy results within the levels of each of the subgroup variables were consistent with those seen in the overall population. In some subgroups there were only small number of subjects, and the results for these subgroups may not be indicative of the overall treatment effects.

Figure 29: Mean Change (±SE) in ICSS from Baseline at Day 84 by Subgroup
(ITT Population, LOCF)

	Placebo		LIF 5.0%		
Phase 2 Study	N	LSM (SE)	N	LSM (SE)	Difference (95% CI)
Overall : Overall	55	0.35 (0.093)	54	0.10 (0.094)	-0.25 (-0.51, 0.02)
Sex : Female	44	0.35 (0.101)	44	0.07 (0.101)	-0.29 (-0.58, -0.00)
Sex : Male	11	0.31 (0.253)	10	0.26 (0.265)	-0.05 (-0.83, 0.72)
Age : <65	38	0.26 (0.099)	34	-0.04 (0.104)	-0.29 (-0.58, -0.01)
Age : >=65	17	0.58 (0.203)	20	0.31 (0.186)	-0.27 (-0.86, 0.31)
Race : White	51	0.40 (0.099)	49	0.10 (0.101)	-0.31 (-0.59, -0.02)
Race : Black or African American	3	-0.50 (0.150)	2	0.25 (0.187)	0.75 (-0.33, 1.83)
Race : Other	1	0.00 (NA)	3	0.00 (NA)	0.00 (NA , NA)
Artificial Tear Use : No	26	0.12 (0.134)	26	0.13 (0.134)	0.01 (-0.37, 0.39)
Artificial Tear Use : Yes	29	0.60 (0.127)	28	0.03 (0.130)	-0.57 (-0.94, -0.19)
ATU & EDS>=40 : No	33	0.21 (0.121)	30	0.13 (0.127)	-0.08 (-0.43, 0.27)
ATU & EDS>=40 : Yes	22	0.58 (0.145)	24	0.03 (0.139)	-0.56 (-0.97, -0.14)
OPUS-1 Study					
Overall : Overall	294	0.16 (0.047)	293	-0.07 (0.047)	-0.23 (-0.36, -0.10)
Sex : Female	216	0.15 (0.056)	229	-0.07 (0.054)	-0.22 (-0.38, -0.07)
Sex : Male	78	0.20 (0.089)	64	-0.06 (0.098)	-0.26 (-0.53, 0.00)
Age : <65	177	0.15 (0.059)	194	-0.05 (0.056)	-0.20 (-0.36, -0.04)
Age : >=65	117	0.17 (0.079)	99	-0.08 (0.086)	-0.25 (-0.48, -0.02)
Race : White	275	0.16 (0.049)	270	-0.06 (0.049)	-0.22 (-0.36, -0.08)
Race : Black or African American	11	0.06 (0.255)	16	-0.29 (0.209)	-0.34 (-1.04, 0.36)
Race : Other	8	0.41 (0.356)	7	0.17 (0.381)	-0.24 (-1.44, 0.96)
Artificial Tear Use : No	166	0.17 (0.059)	165	-0.04 (0.059)	-0.21 (-0.37, -0.04)
Artificial Tear Use : Yes	128	0.15 (0.076)	128	-0.09 (0.076)	-0.24 (-0.46, -0.03)
ATU & EDS >= 40 : No	227	0.14 (0.052)	230	-0.09 (0.052)	-0.24 (-0.38, -0.09)
ATU & EDS >= 40 : Yes	67	0.21 (0.108)	63	0.03 (0.111)	-0.18 (-0.49, 0.13)
OPUS-2 Study					
Overall : Overall	360	-0.70 (0.047)	358	-0.74 (0.047)	-0.03 (-0.16, 0.10)
Sex : Female	265	-0.71 (0.055)	285	-0.76 (0.053)	-0.05 (-0.20, 0.10)
Sex : Male	95	-0.67 (0.092)	73	-0.65 (0.105)	0.03 (-0.25, 0.30)
Age : <65	225	-0.76 (0.058)	236	-0.77 (0.057)	-0.01 (-0.17, 0.15)
Age : >=65	135	-0.61 (0.079)	122	-0.67 (0.083)	-0.06 (-0.28, 0.17)
Race : White	305	-0.73 (0.051)	303	-0.72 (0.051)	0.00 (-0.14, 0.15)
Race : Black or African American	34	-0.89 (0.149)	30	-0.75 (0.159)	0.14 (-0.31, 0.59)
Race : Other	21	-0.11 (0.188)	25	-0.87 (0.171)	-0.76 (-1.29, -0.23)



LSM: Least Square Mean; SE: Standard Error; LIF 5.0%: Lifitegrast Ophthalmic Solution 5.0%.
LSM (SE) were derived from ANCOVA model that adjusted for the baseline ICS score in the phase 2 study and for the baseline and stratification factors in the OPUS-1 and OPUS-2 studies.
ATU: Artifical Tear Use; EDS: Eye Dryness Score

Note that in the subgroup of patients with a history of ATU in the Phase 2 study, LIF 5.0% showed numerically larger reduction in ICSS compared with Placebo; in this subgroup, the treatment difference was -0.57 (95% CI: -0.94, -0.19).

Figure 30: Mean Change (±SE) in VR_OSDI from Baseline at Day 84 by Subgroup (ITT Population, LOCF)

Phase 2 Study	Placebo N	Placebo LSM (SE)	LIF 5.0% N	LIF 5.0% LSM (SE)	Difference (95% CI)
Overall : Overall	55	0.03 (0.116)	54	-0.27 (0.117)	-0.30 (-0.63, 0.03)
Sex : Female	44	0.04 (0.130)	44	-0.15 (0.130)	-0.19 (-0.56, 0.18)
Sex : Male	11	-0.03 (0.239)	10	-0.71 (0.251)	-0.67 (-1.40, 0.06)
Age : <65	38	0.01 (0.144)	34	-0.26 (0.152)	-0.27 (-0.69, 0.15)
Age : >=65	17	0.08 (0.191)	20	-0.28 (0.176)	-0.36 (-0.89, 0.17)
Race : White	51	-0.05 (0.118)	49	-0.24 (0.121)	-0.18 (-0.52, 0.15)
Race : Black or African American	3	1.46 (1.081)	2	-0.94 (1.551)	-2.39 (-13.09, 8.31)
Race : Other	1	0.38 (0.187)	3	-0.46 (0.104)	-0.84 (-3.62, 1.95)
Artificial Tear Use : No	26	0.26 (0.177)	26	-0.32 (0.177)	-0.58 (-1.09, -0.08)
Artificial Tear Use : Yes	29	-0.20 (0.150)	28	-0.18 (0.153)	0.02 (-0.42, 0.45)
OPUS-1 Study					
Overall : Overall	295	-0.11 (0.039)	292	-0.12 (0.039)	-0.01 (-0.12, 0.10)
Sex : Female	217	-0.12 (0.046)	228	-0.16 (0.045)	-0.04 (-0.17, 0.08)
Sex : Male	78	-0.06 (0.075)	64	-0.01 (0.083)	0.05 (-0.17, 0.27)
Age : <65	178	-0.19 (0.050)	193	-0.17 (0.048)	0.02 (-0.12, 0.16)
Age : >=65	117	0.00 (0.063)	99	-0.02 (0.068)	-0.02 (-0.21, 0.16)
Race : White	276	-0.09 (0.040)	269	-0.12 (0.040)	-0.04 (-0.15, 0.07)
Race : Black or African American	11	-0.48 (0.199)	16	-0.12 (0.163)	0.37 (-0.18, 0.91)
Race : Other	8	-0.36 (0.443)	7	-0.03 (0.475)	0.32 (-1.17, 1.81)
Artificial Tear Use : No	166	-0.12 (0.052)	165	-0.12 (0.053)	0.00 (-0.14, 0.15)
Artificial Tear Use : Yes	129	-0.09 (0.059)	127	-0.12 (0.059)	-0.03 (-0.20, 0.13)
OPUS-2 Study					
Overall : Overall	359	-0.28 (0.048)	357	-0.55 (0.048)	-0.28 (-0.41, -0.14)
Sex : Female	265	-0.26 (0.056)	284	-0.55 (0.055)	-0.29 (-0.44, -0.13)
Sex : Male	94	-0.31 (0.090)	73	-0.58 (0.102)	-0.27 (-0.54, 0.00)
Age : <65	224	-0.29 (0.060)	236	-0.59 (0.059)	-0.30 (-0.47, -0.13)
Age : >=65	135	-0.26 (0.080)	121	-0.49 (0.085)	-0.23 (-0.46, -0.00)
Race : White	304	-0.28 (0.052)	302	-0.53 (0.052)	-0.26 (-0.40, -0.11)
Race : Black or African American	34	-0.55 (0.162)	30	-0.84 (0.173)	-0.29 (-0.78, 0.20)
Race : Other	21	0.11 (0.204)	25	-0.40 (0.186)	-0.51 (-1.09, 0.06)

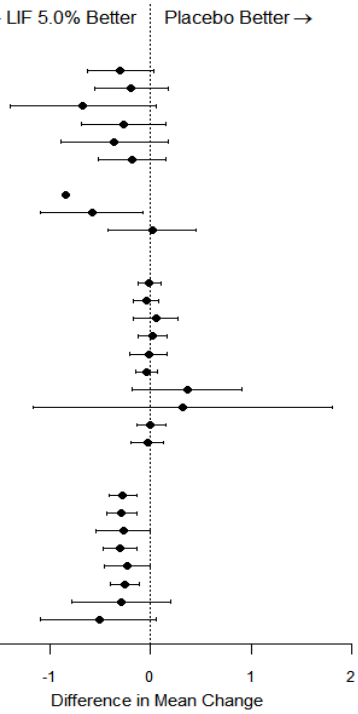
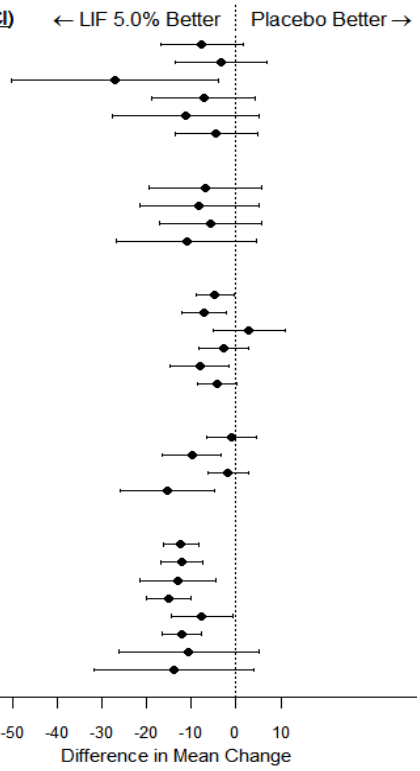


Figure 31: Mean Change (±SE) in EDS from Baseline at Day 84 by Subgroup (ITT Population, LOCF)

Phase 2 Study	Placebo N	Placebo LSM (SE)	LIF 5.0% N	LIF 5.0% LSM (SE)	Difference (95% CI)
Overall : Overall	55	-7.70 (3.240)	53	-15.33 (3.301)	-7.63 (-16.80, 1.54)
Sex : Female	44	-10.46 (3.592)	43	-13.79 (3.633)	-3.33 (-13.49, 6.84)
Sex : Male	11	4.19 (7.420)	10	-22.91 (7.797)	-27.10 (-50.14, -4.06)
Age : <65	38	-8.91 (3.952)	33	-16.11 (4.242)	-7.20 (-18.79, 4.39)
Age : >=65	17	-3.78 (5.884)	20	-15.08 (5.413)	-11.30 (-27.76, 5.16)
Race : White	51	-9.95 (3.198)	48	-14.33 (3.297)	-4.38 (-13.50, 4.74)
Race : Black or African American	3	22.58 (7.829)	2	-48.87 (9.830)	-71.45 (NA, NA)
Race : Other	1	49.90 (119.13)	3	-20.30 (49.065)	-70.19 (NA, NA)
Artificial Tear Use : No	26	-2.90 (4.423)	25	-9.78 (4.511)	-6.89 (-19.59, 5.82)
Artificial Tear Use : Yes	29	-12.05 (4.678)	28	-20.23 (4.761)	-8.18 (-21.57, 5.20)
ATU & EDS >=40 : No	33	-2.63 (3.888)	29	-8.25 (4.148)	-5.62 (-17.0, 5.76)
ATU & EDS >=40 : Yes	22	-14.0 (5.614)	24	-25.1 (5.371)	-11.10 (-26.9, 4.68)
OPUS-1 Study					
Overall : Overall	295	-10.86 (1.530)	293	-15.55 (1.536)	-4.68 (-8.94, -0.43)
Sex : Female	217	-9.99 (1.839)	229	-17.17 (1.790)	-7.19 (-12.23, -2.14)
Sex : Male	78	-13.02 (2.689)	64	-10.07 (2.970)	2.95 (-4.99, 10.89)
Age : <65	178	-12.00 (2.058)	194	-14.71 (1.971)	-2.71 (-8.32, 2.90)
Age : >=65	117	-9.09 (2.259)	99	-17.22 (2.459)	-8.13 (-14.77, -1.50)
Race : White	276	-11.23 (1.564)	270	-15.44 (1.581)	-4.21 (-8.58, 0.16)
Race : Black or African American	11	2.63 (8.064)	16	-24.87 (6.633)	-27.50 (-49.66, -5.34)
Race : Other	8	-8.74 (12.527)	7	-7.73 (13.417)	1.01 (-41.09, 43.11)
Artificial Tear Use (ATU) : No	166	-12.61 (1.999)	165	-13.49 (2.005)	-0.89 (-6.46, 4.68)
Artificial Tear Use (ATU) : Yes	129	-8.47 (2.365)	128	-18.35 (2.375)	-9.88 (-16.49, -3.27)
ATU and EDS >= 40 : No	228	-7.98 (1.650)	230	-9.71 (1.643)	-1.73 (-6.31, 2.85)
ATU and EDS >= 40 : Yes	67	-21.1 (3.699)	63	-36.4 (3.816)	-15.3 (-25.9, -4.71)
OPUS-2 Study					
Overall : Overall	360	-22.86 (1.450)	358	-35.19 (1.454)	-12.33 (-16.36, -8.30)
Sex : Female	265	-23.58 (1.700)	285	-35.78 (1.639)	-12.20 (-16.84, -7.56)
Sex : Male	95	-20.38 (2.822)	73	-33.47 (3.224)	-13.09 (-21.60, -4.59)
Age : <65	225	-20.12 (1.801)	236	-35.11 (1.759)	-14.98 (-19.93, -10.03)
Age : >=65	135	-27.55 (2.427)	122	-35.20 (2.553)	-7.65 (-14.61, -0.70)
Race : White	305	-23.18 (1.565)	303	-35.23 (1.570)	-12.06 (-16.41, -7.70)
Race : Black or African American	34	-24.12 (5.173)	30	-34.67 (5.531)	-10.55 (-26.23, 5.12)
Race : Other	21	-19.03 (6.286)	25	-32.90 (5.719)	-13.87 (-31.75, 4.01)



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5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES

There are no major statistical issues identified in this submission. The following are minor data and analysis issues identified during the review:

i) Data Issue

In the OPUS-2 study, randomization was stratified by baseline ICSS (≤1.5 versus >1.5) and baseline EDS (≤ 60 versus > 60). The following issues were identified during review of the data:

- A total of 23 subjects (11 in Placebo and 13 in LIF 5.0%) with baseline ICSS > 1.5 were incorrectly categorized as having baseline ICSS ≤ 1.5.
- Eleven subjects (6 in Placebo and 5 in LIF 5.0%) with baseline ICSS <=1.5 were incorrectly categorized as having baseline ICSS > 1.5.
- Eleven subjects (5 in Placebo and 6 in LIF 5.0%) with baseline EDS ≥ 60 were incorrectly categorized as having baseline EDS < 60.
- Four subjects (2 in each treatment group) with baseline EDS < 60 were incorrectly classified as having baseline EDS ≥ 60.

The overall efficacy conclusion remained the same when all analyses using the corrected stratification variable were performed.

ii) Analysis Issue

The applicant primary efficacy analysis approach used in the Phase 2, OPUS-1 and OPUS-2 studies were different. In the Phase 2 study, ANCOVA analysis was used to compare the treatment groups in the primary sign and symptom endpoints; in OPUS-1 study, a two-sample t-test was used; and in OPUS-2 study, a regression (ANOVA) analysis was performed. The applicant primary analyses except in the Phase 2 study did not adjust for the baseline values. Furthermore, the three studies differed in the efficacy endpoint definition: the primary sign endpoint in the Phase 2 study was based on the actual ICSS at Day 84 whereas in the OPUS-1 and in the OPUS-2 studies were based on the change from baseline in ICSS at Day 84.

Therefore, for ease of across study assessment, the statistical reviewer primary analysis approach (for all the studies) used ANCOVA model. In the model, the change from baseline value at Day 84 was used as the response variable, and treatment, baseline value, and the study specific strata (specific for OPUS-1 and OPUS-2) was used as covariates. Note that using the actual or the change from baseline value as a response variable in the ANCOVA model provides the same results for treatment comparison.

Based on the ANCOVA model, the difference in the mean change between the treatment groups was determined using the Least Square Means (LS Means). The default observed margin (OM) option in the LSMEANS statement of the PROC MIXED procedure in SAS was used to account for any imbalance in sample size and in the mean change values across strata.

Furthermore, the statistical reviewer performed unadjusted analyses using the two sample t-test and the non-parametric Wilcoxon rank sum test as sensitivity analysis.

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5.2 COLLECTIVE EVIDENCE

Efficacy evidence to support the superiority of lifitegrast ophthalmic solution 5.0% (LIF 5.0%) administered to the ocular surface as a single drop twice daily to Placebo was based on a Phase 2 dose-ranging study and two pivotal Phase 3 trials (OPUS-1 and OPUS-2). In the Phase 3 studies, co-primary efficacy endpoints were defined for the clinical sign and clinical symptom of dry eye, and a primary clinical sign endpoint was defined in the Phase 2 study. Each study was 14 weeks in duration with 5 study visits and the co-primary endpoints were evaluated at Week 12 (Day 84). The co-primary clinical sign endpoint in each study was the mean change in ICSS from baseline at Day 84. The co-primary clinical symptom endpoint in OPUS-1 study was the mean change in VR_OSDI score from baseline at Day 84 and in OPUS-2 study was the mean change in EDS from baseline at Day 84.

In each study, the treatment differences (*LIF 5.0% minus Placebo*) in the mean changes in ICSS, VR_OSDI, and in EDS were tested using ANCOVA model. In the model, the change from baseline value at Day 84 was used as the response variable, and treatment, baseline value, and the study specific strata (specific for OPUS-1 and OPUS-2) were used as covariates.

Sign Endpoint: Inferior Corneal Staining Score (ICSS):

The change in ICSS from baseline at Day 84 was the primary sign endpoint in each study. Statistical superiority in improving the clinical sign (as measured using ICSS) was demonstrated in OPUS-1 study. On the other hand, LIF 5.0% treated group in the Phase 2 and OPUS-2 studies did not show statistically superior efficacy benefit in improving clinical sign over Placebo.

In OPUS-1 study, LIF 5.0% treated group showed numerically larger mean reduction in ICSS from baseline at Day 84 compared with Placebo treated group, and the treatment difference in the mean change in ICSS at Day 84 was -0.23 (95% CI: - 0.36, -0.09). Statistical significant difference was achieved between the treatment groups (p-value = 0.0007).

In the Phase 2 study, both LIF 5.0% and Placebo treated group did not show mean reduction in ICSS from baseline throughout the study; however, a dose response in the mean change in ICSS was seen at Day 84 (See Figure 9). In this study, the treatment difference in the mean change in ICSS at Day 84 was -0.25 (95% CI: -0.51, 0.02) and not statistically significant (p-value =0.0666). Though not statistically significant, the magnitude of treatment difference seen in this study (-0.25) was very close to what was seen in OPUS-1 study (-0.23); the non-statistical significance result in the Phase 2 study was likely due to smaller sample size compared with OPUS-1 study (note that the p-value in the Phase 2 study was very close to the 5% significance level).

In the OPUS-2 study, both treatment groups showed numerically larger mean reductions in ICSS throughout the study compared with in the Phase 2 and OPUS-1 studies. In this study, the treatment difference in the mean change in ICSS at Day 84 was -0.03 (95% CI: - 0.16, 0.10) and not statistically significant (p-value = 0.6122). It should be noted that the larger mean reduction in ICSS observed in both treatment groups in OPUS-2 study compared with in the Phase 2 and OPUS-1 studies was because of the larger mean baseline score in OPUS-2 study than in the Phase 2 and OPUS-1 studies, and the lack of treatment difference in OPUS-2 study (in subjects with moderate-to-sever symptom) may be attributed to insufficient study duration. Note that the mean baseline ICSS in the Phase 2 and OPUS-1 studies and the mean ICSS at Day 84 in the

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OPUS-2 study (after treatment was received for 84 days) were comparable (See Table 4). Therefore, in order to see any separation between the treatment groups in OPUS-2 study that was seen in the Phase 2 and OPUS-1 studies, longer study duration may be needed.

Symptom Endpoint: Visual-related function subscale of OSDI score (VR_OSDI)

The change in VR_OSDI score from baseline at Day 84 was the co-primary symptom endpoint in OPUS-1 study and was supportive symptom endpoint in the Phase 2 and OPUS-2 studies; thus, confidence intervals and p-values reported in the Phase 2 and OPUS-2 studies were intended for descriptive use.

Statistical superiority in improving clinical symptom (using VR_OSDI score) at Day 84 was not demonstrated in OPUS-1 study. LIF 5.0% treated subjects in OPUS-2 study demonstrated a much larger improvement in VR_OSDI over Placebo while in the Phase 2 study showed amoderate improvement over Placebo.

In OPUS-2 study, LIF 5.0% treated group showed much larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group, and the treatment difference (LIF 5.0% minus Placebo) in the mean change in VR_OSDI score at Day 84 was -0.28 (95% CI: -0.41, -0.14; p-value < 0.0001).

In the Phase 2 study, a dose response in the mean change in VR_OSDI was seen at Day 84 (See Figure 11). In this study, LIF 5.0% treated group showed numerically slightly larger mean reduction in VR_OSDI score from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in VR_OSDI score at Day 84 was -0.30 (95% CI: -0.63, 0.03; p-value = 0.0712).

In the OPUS-1 study, both treatment groups showed small and comparable mean reductions in VR_OSDI score from baseline throughout the study, and the treatment difference (LIF 5.0% minus Placebo) in the mean change in VR_OSDI score at Day 84 was -0.01 (95% CI: -0.12, 0.10) . Statistical significant difference was not achieved in this study (p-value = 0.8261).

Symptom Endpoint: Eye Dryness Score (EDS)

The change in EDS from baseline at Day 84 was the co-primary symptom endpoint in OPUS-2 study and was supportive symptom endpoint in the Phase 2 and OPUS-1 studies; thus, confidence intervals and p-values reported in the Phase 2 and OPUS-1 studies were intended for descriptive use.

Statistical superiority in improving the pre-defined clinical symptom (using EDS) at Day 84 was demonstrated in OPUS-2 study. Both the Phase 2 and OPUS-1 studies showed numerically better improvement in the LIF 5.0% treated subjects over Placebo. Additionally, a dose response improvement of EDS was seen at Day 84 in the Phase 2 study.

In the OPUS-2 study, LIF 5.0% treated group showed much larger mean reduction in EDS from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in EDS at Day 84 was -12.3 (95% CI: -16.4, -8.3) and was strongly statistically significant (p-value < 0.0001).

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In OPUS-1 study, LIF 5.0% treated group showed slightly larger mean reduction in EDS from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in EDS at Day 84 was s -4.7 (95% CI: -8.9, -0.43; p-value = 0.0311). In this study, a much large improvement in EDS at Day 84 was observed in a small subgroup of subjects with a recent history of ATU and with baseline EDS ≥40. In this subgroup, the treatment difference in the mean change in EDS at Day 84 was -15.3 (95% CI: -25.9, -4.7). Note that the OPUS-2 study was designed based on the positive finding observed in this subgroup and used EDS as the primary symptom endpoint.

In the Phase 2 study, LIF 5.0% treated group showed slightly larger mean reduction in EDS from baseline throughout the study compared with Placebo treated group, and the treatment difference in the mean change in EDS at Day 84 was -7.6 (95% CI: -16.8, 1.5; p-value = 0.1021). Note that the likely reason the confidence interval for the treatment difference did not exclude zero was due to the smaller sample size compared to the OPUS-1 study.

5.3 Conclusion and Recommendation

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

Based on the totality of evidence, the statistical reviewer recommends for additional data from an adequate and well controlled study. The study, at a minimum, is expected to demonstrate statistical superiority of the test product over Placebo in improving a pre-defined clinical symptom. Furthermore, the test product in this study, at a minimum, is expected to show numerically better improvement in ICSS over Placebo or demonstrate similar level of reduction in ICSS seen in the OPUS-2 study.

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APPENDIX

Table 12: Mean Change in ICSS from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	1.65 (0.513)	1.77 (0.515)	1.81 (0.599)	1.84 (0.597)	2.40 (0.722)	2.39 (0.763)
Median	2.00	2.00	2.00	2.00	2.50	2.50
(95% CI)	(1.51, 1.78)	(1.63, 1.90)	(1.75, 1.88)	(1.78, 1.91)	(2.33, 2.47)	(2.31, 2.47)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	1.90 (0.760)	1.85 (0.596)	1.90 (0.705)	1.88 (0.704)	1.92 (0.910)	1.91 (0.966)
Median	2.00	2.00	2.00	2.00	2.00	2.00
(95% CI)	(1.69, 2.11)	(1.69, 2.01)	(1.82, 1.98)	(1.80, 1.96)	(1.82, 2.01)	(1.81, 2.01)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.85 (0.686)	1.87 (0.631)	1.79 (0.821)	1.71 (0.802)	1.79 (0.981)	1.70 (1.001)
Median	2.00	2.00	2.00	2.00	2.00	1.50
(95% CI)	(1.66, 2.03)	(1.70, 2.04)	(1.70, 1.89)	(1.61, 1.80)	(1.69, 1.90)	(1.60, 1.81)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	2.05 (0.715)	1.83 (0.680)	1.98 (0.874)	1.77 (0.879)	1.69 (1.010)	1.66 (1.044)
Median	2.00	2.00	2.00	2.00	1.50	1.50
(95% CI)	(1.85, 2.24)	(1.65, 2.02)	(1.88, 2.08)	(1.67, 1.87)	(1.59, 1.80)	(1.55, 1.77)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.25 (0.726)	0.06 (0.541)	0.08 (0.771)	0.04 (0.734)	-0.48 (0.800)	-0.48 (0.804)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
(95% CI)	(0.06, 0.45)	(-0.08, 0.21)	(-0.01, 0.17)	(-0.05, 0.12)	(-0.57, -0.40)	(-0.57, -0.40)
LS Means (SE)	0.23 (0.083)	0.09 (0.084)	0.08 (0.038)	0.05 (0.039)	-0.48 (0.041)	-0.49 (0.041)
Diff.(minus Placebo) (95% CI)		-0.13 (-0.37, 0.10)		-0.03 (-0.14, 0.08)		-0.00 (-0.12, 0.11)
P-value: ANCOVA		0.2591		0.5777		0.9518
P-value: Student T-test		0.1253		0.4783		0.9988
P-value: Wilcoxon Test		0.1575		0.4535		0.9602
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	0.20 (0.711)	0.08 (0.612)	-0.02 (0.893)	-0.14 (0.861)	-0.61 (0.899)	-0.69 (0.918)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
(95% CI)	(0.01, 0.39)	(-0.08, 0.25)	(-0.12, 0.08)	(-0.24, -0.04)	(-0.70, -0.51)	(-0.79, -0.59)
LS Means (SE)	0.16 (0.083)	0.12 (0.084)	-0.03 (0.046)	-0.13 (0.046)	-0.60 (0.046)	-0.69 (0.046)
Diff.(minus Placebo) (95% CI)		-0.04 (-0.28, 0.19)		-0.10 (-0.23, 0.02)		-0.09 (-0.21, 0.04)
P-value: ANCOVA		0.7097		0.1094		0.1756
P-value: Student T-test		0.3611		0.1044		0.2138
P-value: Wilcoxon Test		0.2857		0.0838		0.2642
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.40 (0.802)	0.05 (0.773)	0.17 (0.819)	-0.07 (0.868)	-0.71 (0.943)	-0.73 (0.926)
Median	0.00	0.00	0.00	0.00	-0.50	-0.50
(95% CI)	(0.18, 0.62)	(-0.16, 0.26)	(0.07, 0.26)	(-0.17, 0.03)	(-0.80, -0.61)	(-0.83, -0.64)
LS Means (SE)	0.35 (0.093)	0.10 (0.094)	0.16 (0.047)	-0.07 (0.047)	-0.70 (0.047)	-0.74 (0.047)
Diff.(minus Placebo) (95% CI)		-0.25 (-0.51, 0.02)		-0.23 (-0.36, -0.10)		-0.03 (-0.16, 0.10)
P-value: ANCOVA		0.0666		0.0007		0.6122
P-value: Student T-test		0.0209		0.0007		0.6768
P-value: Wilcoxon Test		0.0384		0.0006		0.7849

Reference ID: 3795926

Table 13: Mean Change in VR_OSDI from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	295	293	360	358
Mean (SD)	0.96 (0.865)	1.16 (1.148)	0.93 (0.958)	0.86 (0.931)	1.38 (1.065)	1.48 (1.062)
Median	1.00	0.75	0.67	0.50	1.25	1.42
(95% CI)	(0.74, 1.19)	(0.86, 1.46)	(0.82, 1.04)	(0.75, 0.96)	(1.27, 1.49)	(1.37, 1.59)
Day 14						
N	55	54	295	293	359	358
Mean (SD)	0.94 (0.983)	0.85 (1.057)	0.84 (0.862)	0.81 (0.895)	1.15 (0.999)	1.15 (1.049)
Median	0.67	0.50	0.67	0.50	1.00	1.00
(95% CI)	(0.68, 1.21)	(0.57, 1.14)	(0.74, 0.94)	(0.70, 0.91)	(1.05, 1.26)	(1.04, 1.26)
Day 42						
N	55	53	294	293	360	357
Mean (SD)	0.92 (0.924)	0.98 (1.041)	0.82 (0.878)	0.75 (0.850)	1.11 (1.044)	1.01 (1.053)
Median	0.50	0.75	0.50	0.50	1.00	0.67
(95% CI)	(0.67, 1.16)	(0.69, 1.27)	(0.72, 0.92)	(0.65, 0.85)	(1.00, 1.22)	(0.90, 1.12)
Day 84						
N	55	54	295	292	359	357
Mean (SD)	1.05 (1.173)	0.88 (0.961)	0.80 (0.838)	0.75 (0.861)	1.13 (1.047)	0.90 (0.998)
Median	0.67	0.67	0.50	0.50	1.00	0.50
(95% CI)	(0.74, 1.37)	(0.62, 1.14)	(0.71, 0.90)	(0.65, 0.85)	(1.03, 1.24)	(0.80, 1.01)
Change from Baseline to Day 14						
N	55	54	295	293	359	358
Mean (SD)	-0.04 (0.696)	-0.33 (0.910)	-0.09 (0.754)	-0.05 (0.744)	-0.23 (0.936)	-0.33 (0.986)
Median	0.00	0.00	0.00	0.00	0.00	-0.25
(95% CI)	(-0.23, 0.15)	(-0.58, -0.08)	(-0.18, -0.00)	(-0.14, 0.03)	(-0.32, -0.13)	(-0.44, -0.23)
LS Means (SE)	-0.07 (0.100)	-0.30 (0.101)	-0.08 (0.038)	-0.06 (0.038)	-0.25 (0.044)	-0.31 (0.044)
Diff.(minus Placebo) (95% CI)		-0.22 (-0.51, 0.06)		0.01 (-0.09, 0.12)		-0.06 (-0.18, 0.06)
P-value: ANCOVA		0.1236		0.8227		0.3250
P-value: Student T-test		0.0690		0.5380		0.1300
P-value: Wilcoxon Test		0.0462		0.6999		0.0272
Change from Baseline to Day 42						
N	55	53	294	293	360	357
Mean (SD)	-0.07 (0.738)	-0.22 (0.918)	-0.11 (0.777)	-0.11 (0.789)	-0.27 (1.016)	-0.48 (1.015)
Median	0.00	0.00	0.00	0.00	0.00	-0.33
(95% CI)	(-0.27, 0.13)	(-0.48, 0.03)	(-0.20, -0.02)	(-0.20, -0.02)	(-0.37, -0.16)	(-0.59, -0.38)
LS Means (SE)	-0.11 (0.100)	-0.18 (0.102)	-0.09 (0.039)	-0.12 (0.039)	-0.29 (0.047)	-0.46 (0.047)
Diff.(minus Placebo) (95% CI)		-0.07 (-0.36, 0.21)		-0.03 (-0.14, 0.08)		-0.16 (-0.29, -0.03)
P-value: ANCOVA		0.6089		0.5921		0.0149
P-value: Student T-test		0.3346		0.9976		0.0049
P-value: Wilcoxon Test		0.2761		0.7808		0.0017
Change from Baseline to Day 84						
N	55	54	295	292	359	357
Mean (SD)	0.07 (0.929)	-0.30 (0.934)	-0.12 (0.762)	-0.11 (0.829)	-0.25 (1.069)	-0.58 (1.100)
Median	0.00	0.00	0.00	0.00	0.00	-0.50
(95% CI)	(-0.18, 0.32)	(-0.56, -0.05)	(-0.21, -0.04)	(-0.20, -0.01)	(-0.36, -0.14)	(-0.70, -0.47)
LS Means (SE)	0.03 (0.116)	-0.27 (0.117)	-0.11 (0.039)	-0.12 (0.039)	-0.28 (0.048)	-0.55 (0.048)
Diff.(minus Placebo) (95% CI)		-0.30 (-0.63, 0.03)		-0.01 (-0.12, 0.10)		-0.28 (-0.41, -0.14)
P-value: ANCOVA		0.0712		0.8261		<0.0001
P-value: Student T-test		0.0394		0.7860		<0.0001
P-value: Wilcoxon Test		0.0393		0.9063		<0.0001

Reference ID: 3795926

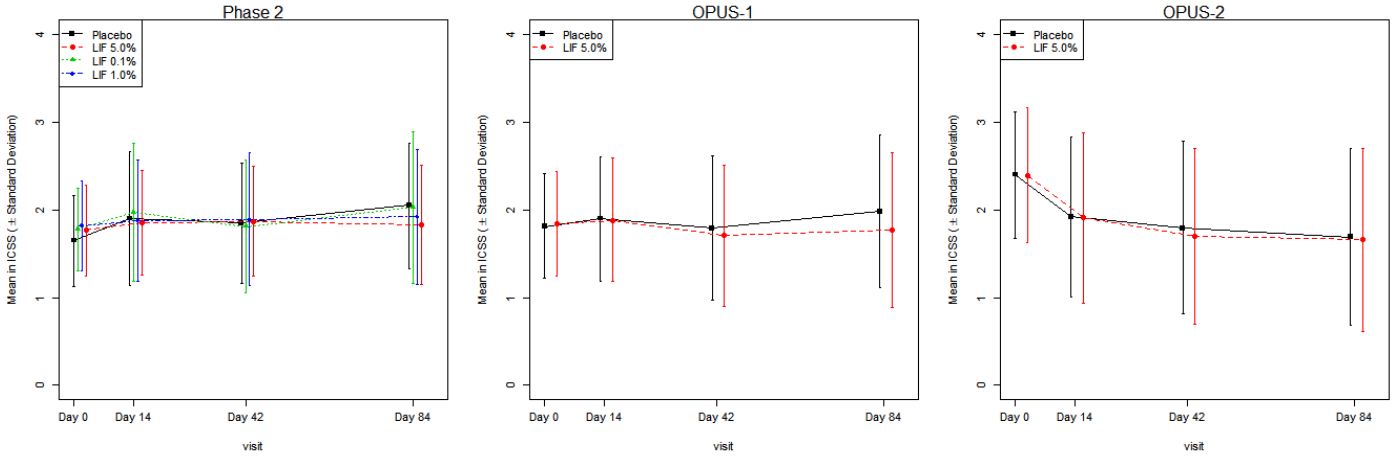
Table 14: Mean Change in EDS from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	57	295	293	360	358
Mean (SD)	51.81 (23.552)	51.58 (24.688)	41.62 (29.690)	40.18 (28.645)	69.22 (16.761)	69.68 (16.954)
Median	55.00	51.00	39.00	42.00	69.00	69.00
(95% CI)	(45.62, 58.00)	(45.03, 58.13)	(38.22, 45.02)	(36.88, 43.47)	(67.48, 70.95)	(67.92, 71.44)
Day 14						
N	54	54	295	293	360	358
Mean (SD)	47.48 (26.258)	42.37 (25.658)	34.13 (29.540)	33.44 (29.116)	56.24 (26.096)	50.20 (26.455)
Median	45.50	42.50	26.00	25.00	60.00	51.00
(95% CI)	(40.31, 54.65)	(35.37, 49.37)	(30.75, 37.52)	(30.10, 36.79)	(53.54, 58.95)	(47.45, 52.95)
Day 42						
N	55	54	295	293	360	358
Mean (SD)	43.27 (24.076)	33.61 (24.911)	32.48 (30.421)	27.56 (28.664)	51.23 (28.121)	41.31 (28.266)
Median	45.00	28.00	24.00	15.00	51.50	40.50
(95% CI)	(36.76, 49.78)	(26.81, 40.41)	(29.00, 35.97)	(24.27, 30.86)	(48.32, 54.15)	(38.37, 44.25)
Day 84						
N	55	54	295	293	360	358
Mean (SD)	44.11 (27.130)	37.06 (27.578)	30.39 (30.773)	25.00 (28.870)	46.47 (29.875)	34.39 (27.862)
Median	47.00	35.00	19.00	11.00	50.00	28.00
(95% CI)	(36.77, 51.44)	(29.53, 44.58)	(26.86, 33.91)	(21.68, 28.32)	(43.37, 49.56)	(31.49, 37.28)
Change from Baseline to Day 14						
N	54	53	295	293	360	358
Mean (SD)	-4.20 (26.384)	-9.58 (22.396)	-7.49 (29.007)	-6.73 (27.358)	-12.98 (24.102)	-19.48 (26.360)
Median	-2.50	-5.00	-4.00	-4.00	-8.00	-18.00
(95% CI)	(-11.41, 3.00)	(-15.76, -3.41)	(-10.81, -4.16)	(-9.88, -3.59)	(-15.47, -10.48)	(-22.22, -16.74)
LS Means (SE)	-4.36 (3.040)	-9.43 (3.068)	-7.15 (1.446)	-7.07 (1.450)	-13.1 (1.282)	-19.4 (1.285)
Diff.(minus Placebo) (95% CI)		-5.07 (-13.6, 3.49)		0.08 (-3.94, 4.11)		-6.33 (-9.90, -2.77)
P-value: ANCOVA		0.2429		0.9676		0.0005
P-value: Student T-test		0.2584		0.7458		0.0006
P-value: Wilcoxon Test		0.1970		0.8939		0.0002
Change from Baseline to Day 42						
N	55	53	295	293	360	358
Mean (SD)	-8.38 (20.046)	-18.58 (25.426)	-9.14 (30.033)	-12.61 (30.714)	-17.99 (26.603)	-28.37 (27.771)
Median	-5.00	-14.00	-4.00	-9.00	-14.00	-29.00
(95% CI)	(-13.80, -2.96)	(-25.59, -11.58)	(-12.58, -5.70)	(-16.15, -9.08)	(-20.74, -15.23)	(-31.26, -25.48)
LS Means (SE)	-8.54 (2.779)	-18.4 (2.831)	-8.76 (1.525)	-13.0 (1.530)	-18.1 (1.386)	-28.3 (1.389)
Diff.(minus Placebo) (95% CI)		-9.89 (-17.8, -2.02)		-4.24 (-8.48, 0.01)		-10.2 (-14.1, -6.36)
P-value: ANCOVA		0.0143		0.0503		0.0000
P-value: Student T-test		0.0222		0.1659		0.0000
P-value: Wilcoxon Test		0.0360		0.0669		<.0001
Change from Baseline to Day 84						
N	55	53	295	293	360	358
Mean (SD)	-7.55 (25.929)	-15.49 (25.987)	-11.23 (28.783)	-15.17 (31.482)	-22.75 (28.600)	-35.30 (28.400)
Median	-9.00	-7.00	-6.00	-9.00	-20.00	-39.00
(95% CI)	(-14.55, -0.54)	(-22.65, -8.33)	(-14.53, -7.94)	(-18.79, -11.55)	(-25.71, -19.79)	(-38.25, -32.34)
LS Means (SE)	-7.70 (3.240)	-15.3 (3.301)	-10.9 (1.530)	-15.5 (1.536)	-22.9 (1.450)	-35.2 (1.454)
Diff.(minus Placebo) (95% CI)		-7.63 (-16.8, 1.54)		-4.68 (-8.94, -0.43)		-12.3 (-16.4, -8.30)
P-value: ANCOVA		0.1021		0.0311		0.0000
P-value: Student T-test		0.1148		0.1137		0.0000
P-value: Wilcoxon Test		0.2890		0.1376		<.0001

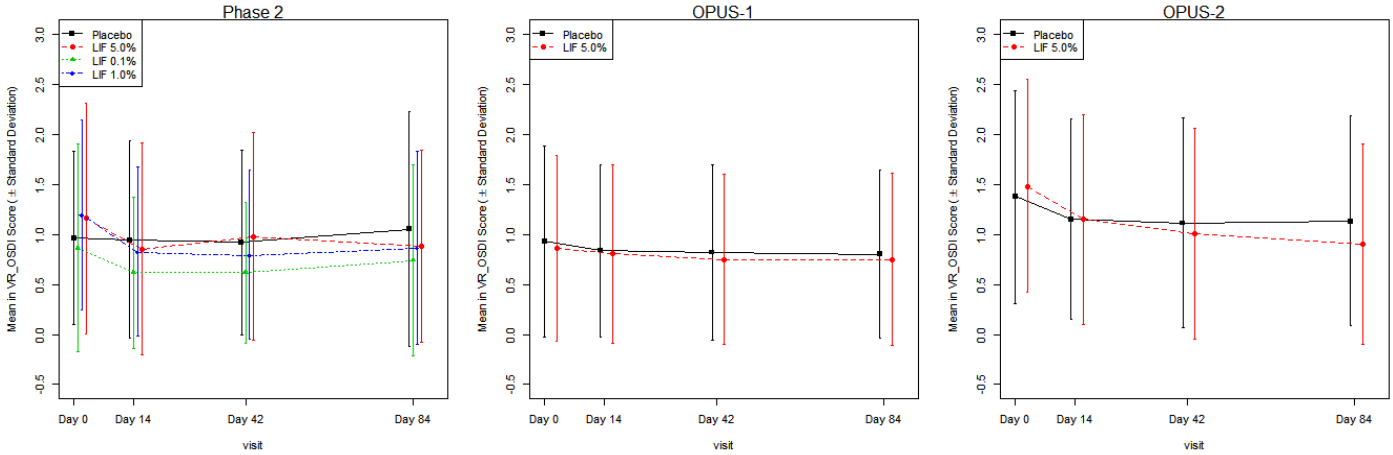
Reference ID: 3795926

Figure 32: Plot of the Actual Mean (± SD) in ICSS, VR_OSDI, and EDS for each Study
(ITT Population, LOCF)

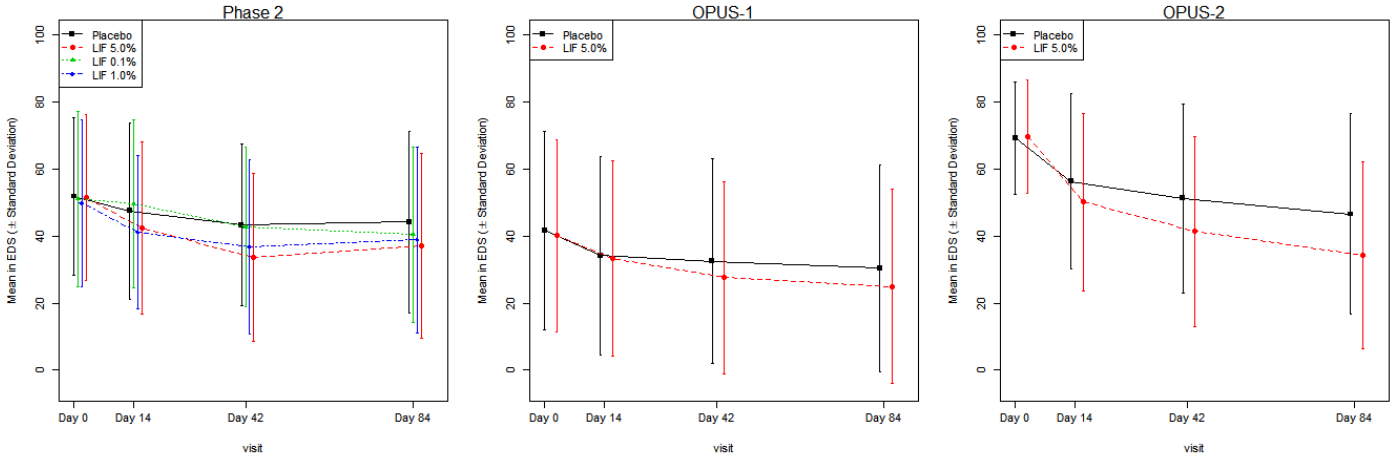
Inferior Corneal Staining Score (ICSS)



Visual-related function subscale of the Ocular Surface Disease Index (VR_OSDI)



Eye Dryness Score (EDS)



Reference ID: 3795926

Table 15: Mean Change in STT from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	4.67 (2.837)	5.02 (2.976)	4.69 (2.855)	4.90 (3.008)	5.12 (2.770)	5.46 (2.827)
Median	4.00	5.00	4.00	4.00	5.00	5.00
(95% CI)	(3.93, 5.42)	(4.23, 5.80)	(4.36, 5.02)	(4.56, 5.25)	(4.84, 5.41)	(5.17, 5.76)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	5.00 (3.621)	6.48 (3.785)	5.66 (5.074)	5.90 (4.815)	6.71 (5.192)	7.23 (5.803)
Median	4.00	7.00	4.00	5.00	5.00	6.00
(95% CI)	(4.02, 5.98)	(5.45, 7.51)	(5.08, 6.24)	(5.35, 6.45)	(6.17, 7.25)	(6.63, 7.84)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	5.76 (5.015)	6.70 (4.777)	6.19 (5.393)	6.63 (5.557)	7.43 (5.832)	7.97 (6.044)
Median	5.00	5.50	5.00	5.00	6.00	6.00
(95% CI)	(4.41, 7.12)	(5.40, 8.01)	(5.57, 6.81)	(5.99, 7.27)	(6.83, 8.04)	(7.34, 8.60)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	5.29 (4.383)	7.00 (5.924)	6.26 (5.598)	6.63 (5.772)	7.41 (5.626)	8.03 (6.248)
Median	4.00	5.50	5.00	5.00	6.00	7.00
(95% CI)	(4.11, 6.48)	(5.38, 8.62)	(5.62, 6.90)	(5.97, 7.30)	(6.82, 7.99)	(7.38, 8.68)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.27 (3.556)	1.50 (3.975)	0.97 (4.620)	1.00 (4.754)	1.59 (4.737)	1.77 (5.371)
Median	0.00	1.00	0.00	0.00	1.00	1.00
(95% CI)	(-0.69, 1.23)	(0.41, 2.59)	(0.44, 1.50)	(0.45, 1.54)	(1.10, 2.08)	(1.21, 2.33)
LS Means (SE)	0.21 (0.465)	1.57 (0.470)	0.93 (0.267)	1.03 (0.268)	1.55 (0.265)	1.81 (0.266)
Diff.(minus Placebo) (95% CI)		1.36 (0.05, 2.67)		0.10 (-0.64, 0.85)		0.26 (-0.48, 1.00)
P-value: ANCOVA		0.0419		0.7861		0.4942
P-value: Student T-test		0.0921		0.9440		0.6301
P-value: Wilcoxon Test		0.0577		0.9766		0.8516
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.04 (4.611)	1.72 (4.414)	1.50 (4.807)	1.73 (5.271)	2.31 (5.308)	2.51 (5.270)
Median	0.00	1.00	0.00	1.00	1.00	1.00
(95% CI)	(-0.21, 2.28)	(0.52, 2.93)	(0.94, 2.05)	(1.12, 2.33)	(1.76, 2.86)	(1.96, 3.06)
LS Means (SE)	1.00 (0.601)	1.76 (0.606)	1.47 (0.291)	1.75 (0.292)	2.31 (0.280)	2.51 (0.280)
Diff.(minus Placebo) (95% CI)		0.76 (-0.93, 2.45)		0.29 (-0.52, 1.10)		0.21 (-0.57, 0.98)
P-value: ANCOVA		0.3753		0.4882		0.6032
P-value: Student T-test		0.4295		0.5803		0.6174
P-value: Wilcoxon Test		0.2122		0.4987		0.5361
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.56 (4.525)	2.02 (6.218)	1.57 (5.072)	1.73 (5.445)	2.28 (5.211)	2.57 (5.606)
Median	0.00	1.00	1.00	1.00	1.00	1.00
(95% CI)	(-0.66, 1.79)	(0.32, 3.72)	(0.99, 2.15)	(1.10, 2.36)	(1.74, 2.82)	(1.98, 3.15)
LS Means (SE)	0.48 (0.690)	2.10 (0.697)	1.55 (0.304)	1.75 (0.305)	2.27 (0.286)	2.58 (0.286)
Diff.(minus Placebo) (95% CI)		1.62 (-0.33, 3.56)		0.21 (-0.64, 1.05)		0.32 (-0.48, 1.11)
P-value: ANCOVA		0.1023		0.6309		0.4331
P-value: Student T-test		0.1648		0.7087		0.4827
P-value: Wilcoxon Test		0.2046		0.7138		0.6142

Reference ID: 3795926

Table 16: Mean Change in Total CSS from Baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	4.43 (1.201)	4.33 (1.062)	4.83 (1.378)	4.84 (1.400)	5.18 (2.014)	5.09 (2.077)
Median	4.25	4.00	4.50	4.50	4.50	4.50
(95% CI)	(4.12, 4.75)	(4.05, 4.61)	(4.67, 4.99)	(4.68, 5.00)	(4.97, 5.39)	(4.88, 5.31)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	4.74 (1.853)	4.33 (1.292)	4.64 (1.764)	4.57 (1.738)	4.05 (2.293)	4.10 (2.339)
Median	5.00	4.00	4.50	4.50	3.50	3.50
(95% CI)	(4.24, 5.24)	(3.98, 4.69)	(4.44, 4.85)	(4.37, 4.77)	(3.82, 4.29)	(3.86, 4.34)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	4.52 (1.481)	4.44 (1.473)	4.34 (1.947)	4.04 (1.947)	3.90 (2.452)	3.63 (2.399)
Median	4.50	4.00	4.00	4.00	3.50	3.00
(95% CI)	(4.12, 4.92)	(4.03, 4.84)	(4.11, 4.56)	(3.82, 4.27)	(3.65, 4.16)	(3.38, 3.88)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	4.80 (1.862)	4.29 (1.439)	4.69 (2.146)	4.30 (2.180)	3.69 (2.459)	3.47 (2.548)
Median	4.50	4.00	4.50	4.00	3.50	3.00
(95% CI)	(4.30, 5.30)	(3.89, 4.68)	(4.45, 4.94)	(4.04, 4.55)	(3.43, 3.94)	(3.21, 3.74)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.29 (1.718)	0.00 (1.124)	-0.19 (1.772)	-0.27 (1.649)	-1.12 (1.773)	-0.99 (1.934)
Median	0.50	0.00	0.00	-0.50	-1.00	-1.00
(95% CI)	(-0.17, 0.76)	(-0.31, 0.31)	(-0.39, 0.01)	(-0.46, -0.09)	(-1.31, -0.94)	(-1.19, -0.79)
LS Means (SE)	0.31 (0.190)	-0.02 (0.192)	-0.19 (0.093)	-0.27 (0.093)	-1.11 (0.094)	-1.00 (0.094)
Diff.(minus Placebo) (95% CI)		-0.33 (-0.86, 0.21)		-0.08 (-0.34, 0.18)		0.11 (-0.15, 0.37)
P-value: ANCOVA		0.2274		0.5317		0.4236
P-value: Student T-test		0.2988		0.5431		0.3510
P-value: Wilcoxon Test		0.1851		0.2653		0.5026
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	0.07 (1.379)	0.10 (1.382)	-0.49 (1.931)	-0.80 (1.909)	-1.28 (2.017)	-1.46 (2.054)
Median	0.00	0.00	-0.50	-0.50	-1.50	-1.50
(95% CI)	(-0.30, 0.45)	(-0.28, 0.48)	(-0.71, -0.27)	(-1.02, -0.58)	(-1.48, -1.07)	(-1.68, -1.25)
LS Means (SE)	0.09 (0.177)	0.08 (0.178)	-0.50 (0.104)	-0.80 (0.104)	-1.26 (0.103)	-1.47 (0.103)
Diff.(minus Placebo) (95% CI)		-0.02 (-0.51, 0.48)		-0.30 (-0.59, -0.01)		-0.21 (-0.50, 0.07)
P-value: ANCOVA		0.9516		0.0411		0.1478
P-value: Student T-test		0.9125		0.0544		0.2181
P-value: Wilcoxon Test		0.9683		0.0329		0.1109
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.35 (1.638)	-0.05 (1.461)	-0.14 (1.923)	-0.55 (1.989)	-1.49 (2.097)	-1.62 (2.043)
Median	0.00	0.00	0.00	-0.50	-1.50	-1.75
(95% CI)	(-0.09, 0.80)	(-0.45, 0.35)	(-0.36, 0.08)	(-0.77, -0.32)	(-1.71, -1.27)	(-1.83, -1.41)
LS Means (SE)	0.37 (0.203)	-0.07 (0.205)	-0.14 (0.112)	-0.55 (0.112)	-1.48 (0.105)	-1.63 (0.106)
Diff.(minus Placebo) (95% CI)		-0.44 (-1.01, 0.13)		-0.41 (-0.72, -0.10)		-0.16 (-0.45, 0.14)
P-value: ANCOVA		0.1285		0.0106		0.2973
P-value: Student T-test		0.1806		0.0117		0.3910
P-value: Wilcoxon Test		0.2538		0.0021		0.2438

Reference ID: 3795926

Table 17: Mean Change in Nasal CLGSS from baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	1.80 (0.932)	1.69 (0.766)	1.90 (0.843)	2.03 (0.814)	2.14 (1.045)	2.13 (1.039)
Median	2.00	2.00	2.00	2.00	2.50	2.00
(95% CI)	(1.56, 2.05)	(1.49, 1.89)	(1.80, 1.99)	(1.94, 2.12)	(2.03, 2.25)	(2.02, 2.23)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	1.83 (1.033)	1.81 (0.803)	1.94 (0.866)	1.89 (0.815)	1.92 (1.045)	1.97 (1.072)
Median	2.00	2.00	2.00	2.00	2.00	2.00
(95% CI)	(1.55, 2.11)	(1.59, 2.02)	(1.84, 2.04)	(1.80, 1.99)	(1.81, 2.02)	(1.86, 2.08)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.67 (0.949)	1.77 (0.856)	1.89 (0.850)	1.84 (0.838)	1.89 (1.080)	1.83 (1.065)
Median	2.00	2.00	2.00	2.00	2.00	2.00
(95% CI)	(1.42, 1.93)	(1.53, 2.00)	(1.80, 1.99)	(1.74, 1.94)	(1.78, 2.00)	(1.72, 1.94)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	1.83 (1.051)	1.83 (0.890)	1.85 (0.919)	1.80 (0.830)	1.86 (1.090)	1.88 (1.091)
Median	2.00	2.00	2.00	2.00	2.00	1.75
(95% CI)	(1.54, 2.11)	(1.59, 2.08)	(1.74, 1.95)	(1.70, 1.89)	(1.75, 1.98)	(1.76, 1.99)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	0.05 (0.743)	0.14 (0.655)	0.04 (0.671)	-0.14 (0.710)	-0.22 (0.743)	-0.16 (0.861)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.15, 0.26)	(-0.04, 0.32)	(-0.04, 0.12)	(-0.22, -0.05)	(-0.30, -0.15)	(-0.25, -0.07)
LS Means (SE)	0.07 (0.091)	0.13 (0.092)	0.02 (0.037)	-0.11 (0.037)	-0.22 (0.039)	-0.16 (0.039)
Diff.(minus Placebo) (95% CI)		0.06 (-0.20, 0.31)		-0.13 (-0.24, -0.03)		0.06 (-0.05, 0.17)
P-value: ANCOVA		0.6520		0.0114		0.2835
P-value: Student T-test		0.5312		0.0020		0.2837
P-value: Wilcoxon Test		0.2745		0.0036		0.4304
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	-0.10 (0.655)	0.10 (0.716)	-0.00 (0.749)	-0.19 (0.757)	-0.25 (0.766)	-0.29 (0.933)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.28, 0.08)	(-0.09, 0.30)	(-0.09, 0.08)	(-0.27, -0.10)	(-0.33, -0.17)	(-0.39, -0.20)
LS Means (SE)	-0.09 (0.088)	0.09 (0.089)	-0.03 (0.040)	-0.16 (0.040)	-0.25 (0.042)	-0.30 (0.042)
Diff.(minus Placebo) (95% CI)		0.17 (-0.07, 0.42)		-0.14 (-0.25, -0.02)		-0.05 (-0.16, 0.07)
P-value: ANCOVA		0.1672		0.0164		0.4087
P-value: Student T-test		0.1276		0.0029		0.4831
P-value: Wilcoxon Test		0.2106		0.0019		0.2679
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	0.05 (0.711)	0.17 (0.818)	-0.05 (0.743)	-0.23 (0.776)	-0.27 (0.805)	-0.25 (0.850)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.14, 0.25)	(-0.06, 0.39)	(-0.14, 0.03)	(-0.32, -0.14)	(-0.36, -0.19)	(-0.34, -0.16)
LS Means (SE)	0.07 (0.100)	0.15 (0.101)	-0.07 (0.041)	-0.21 (0.041)	-0.27 (0.041)	-0.25 (0.041)
Diff.(minus Placebo) (95% CI)		0.09 (-0.20, 0.37)		-0.14 (-0.25, -0.02)		0.02 (-0.09, 0.14)
P-value: ANCOVA		0.5472		0.0195		0.7118
P-value: Student T-test		0.4467		0.0037		0.6858
P-value: Wilcoxon Test		0.3952		0.0055		0.7598

Reference ID: 3795926

Table 18: Mean Change in Total OSDI Score from baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	295	293	360	358
Mean (SD)	28.84 (16.499)	31.77 (21.312)	27.05 (18.147)	26.03 (19.042)	39.83 (20.435)	40.78 (21.845)
Median	29.58	27.29	22.73	20.83	39.58	37.50
(95% CI)	(24.50, 33.17)	(26.16, 37.37)	(24.97, 29.13)	(23.84, 28.22)	(37.71, 41.95)	(38.51, 43.05)
Day 14						
N	55	54	295	293	360	358
Mean (SD)	29.43 (18.937)	27.49 (19.441)	24.71 (17.625)	24.70 (17.781)	34.87 (20.298)	33.66 (21.587)
Median	22.92	21.16	20.45	20.45	31.82	29.17
(95% CI)	(24.31, 34.55)	(22.18, 32.79)	(22.69, 26.73)	(22.65, 26.74)	(32.77, 36.98)	(31.42, 35.91)
Day 42						
N	55	54	295	293	360	358
Mean (SD)	27.98 (18.033)	29.39 (19.676)	23.78 (17.844)	23.63 (17.860)	33.85 (21.090)	30.59 (22.676)
Median	25.00	25.00	19.44	20.00	31.25	25.00
(95% CI)	(23.10, 32.85)	(24.02, 34.76)	(21.74, 25.83)	(21.58, 25.69)	(31.66, 36.03)	(28.23, 32.94)
Day 84						
N	55	54	295	293	360	358
Mean (SD)	29.43 (20.906)	27.99 (20.732)	23.21 (17.239)	23.05 (18.268)	32.14 (22.192)	27.01 (21.763)
Median	25.00	22.36	20.00	18.75	28.47	22.50
(95% CI)	(23.77, 35.08)	(22.33, 33.65)	(21.24, 25.19)	(20.95, 25.15)	(29.84, 34.44)	(24.75, 29.28)
Change from Baseline to Day 14						
N	55	54	295	293	360	358
Mean (SD)	-0.09 (10.069)	-5.15 (14.149)	-2.34 (14.000)	-1.33 (13.405)	-4.96 (16.373)	-7.12 (19.358)
Median	0.00	-2.18	-2.08	-0.23	-4.17	-4.92
(95% CI)	(-2.81, 2.64)	(-9.01, -1.29)	(-3.94, -0.74)	(-2.87, 0.21)	(-6.66, -3.26)	(-9.13, -5.11)
LS Means (SE)	-0.40 (1.580)	-4.83 (1.595)	-2.18 (0.721)	-1.49 (0.724)	-5.13 (0.851)	-6.95 (0.853)
Diff.(minus Placebo) (95% CI)		-4.44 (-8.89, 0.02)		0.68 (-1.32, 2.69)		-1.82 (-4.18, 0.55)
P-value: ANCOVA		0.0512		0.5035		0.1319
P-value: Student T-test		0.0333		0.3731		0.1067
P-value: Wilcoxon Test		0.1698		0.1891		0.1314
Change from Baseline to Day 42						
N	55	54	295	293	360	358
Mean (SD)	-1.53 (9.776)	-3.25 (14.629)	-3.27 (14.164)	-2.40 (15.299)	-5.99 (17.799)	-10.20 (19.325)
Median	-2.27	-0.97	-2.27	-2.08	-5.89	-9.09
(95% CI)	(-4.18, 1.11)	(-7.24, 0.74)	(-4.89, -1.64)	(-4.16, -0.64)	(-7.83, -4.14)	(-12.21, -8.19)
LS Means (SE)	-1.88 (1.583)	-2.90 (1.597)	-3.09 (0.769)	-2.58 (0.772)	-6.16 (0.899)	-10.0 (0.901)
Diff.(minus Placebo) (95% CI)		-1.02 (-5.48, 3.45)		0.51 (-1.63, 2.65)		-3.86 (-6.36, -1.37)
P-value: ANCOVA		0.6529		0.6416		0.0025
P-value: Student T-test		0.4728		0.4752		0.0025
P-value: Wilcoxon Test		0.8748		0.5792		0.0012
Change from Baseline to Day 84						
N	55	54	295	293	360	358
Mean (SD)	-0.09 (13.633)	-4.65 (15.223)	-3.84 (14.949)	-2.98 (15.250)	-7.69 (20.247)	-13.77 (21.255)
Median	-1.14	-1.59	-2.50	-1.67	-6.25	-12.41
(95% CI)	(-3.77, 3.60)	(-8.80, -0.49)	(-5.55, -2.12)	(-4.73, -1.22)	(-9.79, -5.59)	(-15.98, -11.56)
LS Means (SE)	-0.38 (1.896)	-4.34 (1.914)	-3.65 (0.783)	-3.17 (0.786)	-7.91 (0.979)	-13.6 (0.981)
Diff.(minus Placebo) (95% CI)		-3.96 (-9.31, 1.39)		0.48 (-1.70, 2.65)		-5.64 (-8.36, -2.92)
P-value: ANCOVA		0.1451		0.6686		0.0001
P-value: Student T-test		0.1023		0.4904		0.0001
P-value: Wilcoxon Test		0.1905		0.5056		<.0001

Reference ID: 3795926

Table 19: Mean Change in ODS Score from baseline by Visit
(ITT Population, LOCF)

	Phase 2		OPUS-1		OPUS-2	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline						
N	58	58	294	293	360	358
Mean (SD)	2.03 (1.169)	2.03 (1.042)	1.78 (1.161)	1.66 (1.191)	2.29 (1.080)	2.30 (1.030)
Median	2.00	2.00	2.00	2.00	3.00	2.00
(95% CI)	(1.73, 2.34)	(1.76, 2.31)	(1.65, 1.91)	(1.52, 1.79)	(2.18, 2.40)	(2.19, 2.41)
Day 14						
N	55	54	294	293	360	358
Mean (SD)	1.82 (1.234)	1.76 (1.164)	1.49 (1.159)	1.47 (1.127)	1.99 (1.175)	1.95 (1.160)
Median	2.00	1.00	1.00	1.00	2.00	2.00
(95% CI)	(1.48, 2.15)	(1.44, 2.08)	(1.36, 1.63)	(1.34, 1.60)	(1.87, 2.11)	(1.83, 2.07)
Day 42						
N	55	54	294	293	360	358
Mean (SD)	1.71 (1.083)	1.41 (1.073)	1.35 (1.178)	1.27 (1.187)	1.89 (1.188)	1.66 (1.200)
Median	2.00	1.00	1.00	1.00	2.00	2.00
(95% CI)	(1.42, 2.00)	(1.11, 1.70)	(1.21, 1.48)	(1.13, 1.41)	(1.77, 2.01)	(1.53, 1.78)
Day 84						
N	55	54	294	293	360	358
Mean (SD)	1.67 (1.037)	1.46 (1.177)	1.31 (1.182)	1.10 (1.153)	1.72 (1.233)	1.39 (1.124)
Median	2.00	1.50	1.00	1.00	2.00	1.00
(95% CI)	(1.39, 1.95)	(1.14, 1.78)	(1.18, 1.45)	(0.97, 1.23)	(1.59, 1.85)	(1.27, 1.51)
Change from Baseline to Day 14						
N	55	54	294	293	360	358
Mean (SD)	-0.22 (1.066)	-0.30 (1.283)	-0.29 (1.337)	-0.19 (1.283)	-0.30 (1.215)	-0.35 (1.239)
Median	0.00	0.00	0.00	0.00	0.00	0.00
(95% CI)	(-0.51, 0.07)	(-0.65, 0.05)	(-0.44, -0.13)	(-0.34, -0.04)	(-0.43, -0.18)	(-0.48, -0.22)
LS Means (SE)	-0.22 (0.143)	-0.29 (0.144)	-0.25 (0.062)	-0.23 (0.062)	-0.30 (0.057)	-0.35 (0.057)
Diff.(minus Placebo) (95% CI)		-0.07 (-0.47, 0.33)		0.02 (-0.16, 0.19)		-0.05 (-0.20, 0.11)
P-value: ANCOVA		0.7345		0.8368		0.5676
P-value: Student T-test		0.7301		0.3654		0.5914
P-value: Wilcoxon Test		0.5350		0.4113		0.6046
Change from Baseline to Day 42						
N	55	54	294	293	360	358
Mean (SD)	-0.33 (1.037)	-0.65 (1.320)	-0.43 (1.343)	-0.39 (1.357)	-0.40 (1.245)	-0.64 (1.327)
Median	0.00	-1.00	0.00	0.00	0.00	-1.00
(95% CI)	(-0.61, -0.05)	(-1.01, -0.29)	(-0.59, -0.28)	(-0.54, -0.23)	(-0.53, -0.27)	(-0.78, -0.50)
LS Means (SE)	-0.33 (0.133)	-0.64 (0.134)	-0.39 (0.065)	-0.43 (0.065)	-0.40 (0.059)	-0.64 (0.059)
Diff.(minus Placebo) (95% CI)		-0.31 (-0.68, 0.07)		-0.03 (-0.21, 0.15)		-0.23 (-0.40, -0.07)
P-value: ANCOVA		0.1050		0.7152		0.0051
P-value: Student T-test		0.1607		0.6778		0.0128
P-value: Wilcoxon Test		0.1865		0.8559		0.0083
Change from Baseline to Day 84						
N	55	54	294	293	360	358
Mean (SD)	-0.36 (1.112)	-0.59 (1.421)	-0.47 (1.379)	-0.56 (1.368)	-0.57 (1.354)	-0.91 (1.280)
Median	0.00	-1.00	0.00	0.00	-1.00	-1.00
(95% CI)	(-0.66, -0.06)	(-0.98, -0.20)	(-0.62, -0.31)	(-0.71, -0.40)	(-0.71, -0.43)	(-1.04, -0.78)
LS Means (SE)	-0.37 (0.141)	-0.59 (0.143)	-0.42 (0.065)	-0.60 (0.065)	-0.57 (0.059)	-0.91 (0.059)
Diff.(minus Placebo) (95% CI)		-0.22 (-0.61, 0.18)		-0.18 (-0.36, 0.01)		-0.34 (-0.50, -0.17)
P-value: ANCOVA		0.2841		0.0572		0.0001
P-value: Student T-test		0.3504		0.4259		0.0006
P-value: Wilcoxon Test		0.4506		0.7462		0.0003

Reference ID: 3795926

Table 20: Mean Change in EDisS Score from Baseline by Visit
(ITT Population, LOCF)

	OPUS-2	
Summary	**Placebo**	**LIF 5.0%**
Baseline		
N	360	358
Mean (SD)	55.53 (24.927)	56.15 (25.386)
Median	56.50	56.00
(95% CI)	(52.95, 58.11)	(53.51, 58.79)
Day 14		
N	360	358
Mean (SD)	45.07 (26.842)	44.12 (28.039)
Median	48.00	48.00
(95% CI)	(42.29, 47.85)	(41.20, 47.03)
Day 42		
N	360	358
Mean (SD)	42.72 (28.737)	36.38 (28.407)
Median	46.00	34.50
(95% CI)	(39.74, 45.70)	(33.42, 39.33)
Day 84		
N	360	358
Mean (SD)	38.80 (30.191)	29.69 (26.432)
Median	39.00	24.00
(95% CI)	(35.67, 41.93)	(26.94, 32.44)
Change from Baseline to Day 14		
N	360	358
Mean (SD)	-10.46 (25.643)	-12.03 (30.105)
Median	-7.00	-8.00
(95% CI)	(-13.12, -7.80)	(-15.16, -8.90)
LS Means (SE)	-10.6 (1.297)	-11.9 (1.300)
Diff.(minus Placebo) (95% CI)		-1.25 (-4.85, 2.36)
P-value: ANCOVA		0.4978
P-value: Student T-test		0.4522
P-value: Wilcoxon Test		0.4481
Change from Baseline to Day 42		
N	360	358
Mean (SD)	-12.81 (29.167)	-19.77 (32.412)
Median	-8.50	-20.50
(95% CI)	(-15.84, -9.79)	(-23.14, -16.40)
LS Means (SE)	-13.0 (1.400)	-19.6 (1.404)
Diff.(minus Placebo) (95% CI)		-6.52 (-10.4, -2.63)
P-value: ANCOVA		0.0011
P-value: Student T-test		0.0026
P-value: Wilcoxon Test		0.0007
Change from Baseline to Day 84		
N	360	358
Mean (SD)	-16.73 (31.207)	-26.46 (31.238)
Median	-14.00	-26.00
(95% CI)	(-19.97, -13.50)	(-29.70, -23.21)
LS Means (SE)	-17.0 (1.413)	-26.2 (1.417)
Diff.(minus Placebo) (95% CI)		-9.28 (-13.2, -5.35)
P-value: ANCOVA		0.0000
P-value: Student T-test		0.0000
P-value: Wilcoxon Test		<.0001

Reference ID: 3795926

Table 21: Mean change (± SE) in EDS by History of ATU and Baseline EDS in OPUS-1
(ITT Population, LOCF)

	ATU & EDS ≥ 40		Other	
Summary	**Placebo**	**LIF 5.0%**	**Placebo**	**LIF 5.0%**
Baseline				
N	67	63	228	230
Mean (SD)	67.82 (18.211)	63.97 (18.542)	33.92 (27.984)	33.66 (27.474)
Median	61.00	58.00	26.00	27.00
(95% CI)	(63.38, 72.26)	(59.30, 68.64)	(30.27, 37.57)	(30.09, 37.23)
Day 14				
N	67	63	228	230
Mean (SD)	45.82 (30.343)	43.57 (28.692)	30.70 (28.466)	30.67 (28.672)
Median	50.00	44.00	22.50	21.00
(95% CI)	(38.42, 53.22)	(36.35, 50.80)	(26.98, 34.41)	(26.94, 34.39)
Day 42				
N	67	63	228	230
Mean (SD)	48.51 (32.859)	32.71 (28.287)	27.77 (28.046)	26.15 (28.666)
Median	51.00	27.00	18.00	12.00
(95% CI)	(40.49, 56.52)	(25.59, 39.84)	(24.11, 31.43)	(22.43, 29.88)
Day 84				
N	67	63	228	230
Mean (SD)	45.76 (33.315)	28.57 (28.072)	25.87 (28.522)	24.03 (29.068)
Median	42.00	21.00	15.00	9.00
(95% CI)	(37.63, 53.89)	(21.50, 35.64)	(22.15, 29.59)	(20.25, 27.80)
Change from Baseline to Day 14				
N	67	63	228	230
Mean (SD)	-22.00 (34.366)	-20.40 (29.463)	-3.22 (25.807)	-2.99 (25.571)
Median	-18.00	-19.00	-2.00	-1.00
(95% CI)	(-30.38, -13.62)	(-27.82, -12.98)	(-6.59, 0.14)	(-6.31, 0.33)
LS Means (SE)	-20.7 (3.619)	-21.8 (3.733)	-3.16 (1.528)	-3.06 (1.521)
Diff.(minus Placebo) (95% CI)		-1.05 (-11.4, 9.29)		0.10 (-4.14, 4.34)
P-value: ANCOVA		0.8412		0.9626
P-value: Student T-test		0.7763		0.9229
P-value: Wilcoxon Test		0.9443		0.8091
Change from Baseline to Day 42				
N	67	63	228	230
Mean (SD)	-19.31 (32.516)	-31.25 (29.648)	-6.15 (28.657)	-7.51 (29.036)
Median	-12.00	-31.00	-3.00	-5.00
(95% CI)	(-27.24, -11.38)	(-38.72, -23.79)	(-9.89, -2.41)	(-11.28, -3.74)
LS Means (SE)	-18.3 (3.670)	-32.3 (3.786)	-6.06 (1.647)	-7.60 (1.640)
Diff.(minus Placebo) (95% CI)		-14.1 (-24.5, -3.57)		-1.54 (-6.11, 3.03)
P-value: ANCOVA		0.0090		0.5083
P-value: Student T-test		0.0308		0.6143
P-value: Wilcoxon Test		0.0166		0.4144
Change from Baseline to Day 84				
N	67	63	228	230
Mean (SD)	-22.06 (31.591)	-35.40 (31.722)	-8.05 (27.168)	-9.63 (29.121)
Median	-24.00	-38.00	-4.00	-5.00
(95% CI)	(-29.77, -14.35)	(-43.39, -27.41)	(-11.60, -4.51)	(-13.42, -5.85)
LS Means (SE)	-21.1 (3.699)	-36.4 (3.816)	-7.98 (1.650)	-9.71 (1.643)
Diff.(minus Placebo) (95% CI)		-15.3 (-25.9, -4.71)		-1.73 (-6.31, 2.85)
P-value: ANCOVA		0.0050		0.4581
P-value: Student T-test		0.0178		0.5481
P-value: Wilcoxon Test		0.0269		0.5078

Reference ID: 3795926

Table 22: Sensitivity Analysis for the Mean Change in Signs and Symptoms from Baseline at Day 84 (Observed Cases)
(ITT Population)

Phase 2

	Parameters	LSM (SE)		Difference in LSM (95% CI)	P-value
		Placebo (N = 47)	LIF 5.0% (N = 48)		
Sign	ICSS	0.30 (0.101)	0.06 (0.100)	-0.24 (-0.52, 0.05)	0.1006
	Nasal CLGSS	0.05 (0.106)	0.20 (0.105)	0.15 (-0.15, 0.44)	0.3325
	STT	0.36 (0.796)	2.05 (0.779)	1.69 (-0.53, 3.90)	0.1333
	Total CSS	0.45 (0.221)	-0.06 (0.219)	-0.51 (-1.13, 0.11)	0.1071
Symptom	EDS	-7.53 (3.504)	-15.2 (3.504)	-7.64 (-17.5, 2.20)	0.1266
	TOTAL OSDI	-0.67 (2.100)	-5.18 (2.100)	-4.50 (-10.4, 1.41)	0.1336
	VR_OSDI	0.05 (0.125)	-0.33 (0.125)	-0.37 (-0.73, -0.02)	0.0367
	ODS	-0.33 (0.152)	-0.63 (0.150)	-0.30 (-0.73, 0.12)	0.1608

OPUS-1

	Parameters	Placebo (N = 283)	LIF 5.0% (N = 281)	Difference in LSM (95% CI)	P-value
Sign	ICSS	0.17 (0.048)	-0.08 (0.048)	-0.25 (-0.39, -0.12)	0.0003
	Nasal CLGSS	-0.08 (0.042)	-0.21 (0.042)	-0.13 (-0.25, -0.02)	0.0249
	STT	1.50 (0.312)	1.84 (0.313)	0.34 (-0.53, 1.21)	0.4437
	Total CSS	-0.11 (0.115)	-0.56 (0.116)	-0.45 (-0.77, -0.13)	0.0057
Symptom	EDS	-10.8 (1.575)	-15.8 (1.581)	-4.98 (-9.37, -0.59)	0.0261
	TOTAL OSDI	-3.49 (0.801)	-3.31 (0.805)	0.17 (-2.06, 2.41)	0.8783
	VR_OSDI	-0.10 (0.040)	-0.13 (0.040)	-0.02 (-0.14, 0.09)	0.664
	ODS	-0.42 (0.066)	-0.62 (0.067)	-0.20 (-0.39, -0.02)	0.0317

OPUS-2

	Parameters	Placebo (N = 350)	LIF 5.0% (N = 328)	Difference in LSM (95% CI)	P-value
Sign	ICSS	-0.71 (0.048)	-0.76 (0.049)	-0.05 (-0.18, 0.09)	0.4749
	Nasal CLGSS	-0.28 (0.041)	-0.26 (0.042)	0.02 (-0.09, 0.14)	0.7149
	STT	2.23 (0.289)	2.65 (0.299)	0.42 (-0.40, 1.23)	0.3172
	Total CSS	-1.50 (0.107)	-1.70 (0.110)	-0.20 (-0.50, 0.10)	0.2012
Symptom	EDS	-23.3 (1.444)	-36.9 (1.491)	-13.6 (-17.7, -9.55)	<.0001
	TOTAL OSDI	-8.22 (0.942)	-15.0 (0.973)	-6.77 (-9.43, -4.11)	<.0001
	VR_OSDI	-0.29 (0.046)	-0.62 (0.048)	-0.33 (-0.46, -0.20)	<.0001
	ODS	-0.59 (0.058)	-0.97 (0.060)	-0.39 (-0.55, -0.22)	<.0001
	EDisS	-17.6 (1.393)	-28.2 (1.439)	-10.6 (-14.5, -6.66)	<.0001

ICSS: Inferior corneal staining score; Total CSS: Total corneal staining score; Nasal CLGSS: Nasal conjunctival lissamine green staining score; STT: Schirmer Tear Test (mm/5 minutes); EDS: Eye Dryness Score (VAS); OSDI: Ocular Surface Disease Index; VR OSDI: Vision related OSDI; EDisS: Eye Discomfort Score (VAS); ODS: Ocular Discomfort Score.

LSM: Least Square Mean; SE: Standard Error.

Reference ID: 3795926

Table 23: Sensitivity Analysis for the Mean Change in Signs and Symptoms from Baseline at Day 84 (WOCF)
(ITT Population)

Phase 2

	Parameters	LSM (SE)		Difference in LSM (95% CI)	P-value
		Placebo (N = 58)	LIF 5.0% (N = 58)		
Sign	ICSS	0.34 (0.089)	0.11 (0.089)	-0.23 (-0.48, 0.02)	0.0732
	Nasal CLGSS	0.09 (0.091)	0.19 (0.091)	0.10 (-0.16, 0.35)	0.4489
	STT	0.11 (0.651)	1.66 (0.651)	1.55 (-0.28, 3.37)	0.0961
	Total CSS	0.41 (0.185)	0.05 (0.185)	-0.35 (-0.87, 0.17)	0.1806
Symptom	EDS	-4.55 (3.061)	-12.4 (3.087)	-7.81 (-16.4, 0.80)	0.0750
	TOTAL OSDI	0.29 (1.795)	-3.62 (1.795)	-3.91 (-8.95, 1.12)	0.1265
	VR_OSDI	0.06 (0.108)	-0.21 (0.108)	-0.28 (-0.58, 0.03)	0.0731
	ODS	-0.21 (0.136)	-0.50 (0.136)	-0.29 (-0.68, 0.09)	0.1317

OPUS-1

	Parameters	Placebo (N = 294)	LIF 5.0% (N = 293)	Difference in LSM (95% CI)	P-value
Sign	ICSS	0.18 (0.047)	-0.06 (0.047)	-0.25 (-0.38, -0.11)	0.0002
	Nasal CLGSS	-0.07 (0.041)	-0.20 (0.041)	-0.13 (-0.25, -0.02)	0.0198
	STT	1.41 (0.302)	1.73 (0.302)	0.33 (-0.51, 1.16)	0.4467
	Total CSS	-0.09 (0.111)	-0.51 (0.111)	-0.43 (-0.74, -0.12)	0.0066
Symptom	EDS	-10.7 (1.530)	-15.0 (1.530)	-4.30 (-8.55, -0.05)	0.0476
	TOTAL OSDI	-3.19 (0.781)	-3.10 (0.782)	0.08 (-2.09, 2.25)	0.9392
	VR_OSDI	-0.09 (0.039)	-0.12 (0.039)	-0.03 (-0.14, 0.08)	0.6349
	ODS	-0.40 (0.065)	-0.58 (0.065)	-0.18 (-0.36, -0.00)	0.0492

OPUS-2

	Parameters	Placebo (N = 360)	LIF 5.0% (N = 358)	Difference in LSM (95% CI)	P-value
Sign	ICSS	-0.68 (0.047)	-0.68 (0.048)	0.01 (-0.13, 0.14)	0.9335
	Nasal CLGSS	-0.26 (0.041)	-0.21 (0.041)	0.05 (-0.06, 0.17)	0.3634
	STT	2.16 (0.282)	2.31 (0.282)	0.15 (-0.63, 0.94)	0.7025
	Total CSS	-1.44 (0.106)	-1.52 (0.106)	-0.08 (-0.37, 0.22)	0.6041
Symptom	EDS	-22.2 (1.476)	-33.3 (1.480)	-11.1 (-15.2, -7.01)	<.0001
	TOTAL OSDI	-7.75 (0.987)	-12.7 (0.990)	-4.98 (-7.72, -2.23)	0.0004
	VR_OSDI	-0.27 (0.048)	-0.52 (0.049)	-0.25 (-0.39, -0.12)	0.0002
	ODS	-0.55 (0.059)	-0.86 (0.060)	-0.31 (-0.47, -0.14)	0.0003
	EDisS	-16.6 (1.438)	-24.8 (1.442)	-8.25 (-12.3, -4.26)	<.0001

WOCF: Worst observation carried forward.

;

Reference ID: 3795926

Table 24: Sensitivity Analysis for the Mean Change in Signs and Symptoms from Baseline at Day 84 (MRMM Analysis)
(ITT Population)

Phase 2

	Parameters	LSM (SE)		Difference in LSM (95% CI)	P-value
		Placebo (N = 47)	LIF 5.0% (N = 48)		
Sign	ICSS	0.35 (0.106)	0.09 (0.101)	-0.26 (-0.54, 0.02)	0.0721
	Nasal CLGSS	0.01 (0.098)	0.12 (0.114)	0.12 (-0.17, 0.40)	0.4206
	STT	0.30 (0.652)	2.00 (0.898)	1.70 (-0.46, 3.85)	0.1209
	Total CSS	0.40 (0.242)	-0.09 (0.201)	-0.49 (-1.10, 0.11)	0.1105
Symptom	EDS	-7.34 (3.504)	-14.5 (3.654)	-7.15 (-16.8, 2.48)	0.1438
	TOTAL OSDI	0.06 (2.122)	-3.90 (2.151)	-3.96 (-9.75, 1.83)	0.1781
	VR_OSDI	0.07 (0.140)	-0.27 (0.113)	-0.34 (-0.68, 0.00)	0.0530
	ODS	-0.31 (0.134)	-0.58 (0.181)	-0.27 (-0.70, 0.16)	0.2138

OPUS-1

	Parameters	Placebo (N = 283)	LIF 5.0% (N = 281)	Difference in LSM (95% CI)	P-value
Sign	ICSS	0.12 (0.051)	-0.13 (0.054)	-0.24 (-0.38, -0.11)	0.0003
	Nasal CLGSS	-0.14 (0.047)	-0.28 (0.046)	-0.14 (-0.26, -0.03)	0.0134
	STT	1.74 (0.330)	2.07 (0.358)	0.33 (-0.52, 1.19)	0.4409
	Total CSS	-0.25 (0.121)	-0.71 (0.125)	-0.46 (-0.76, -0.15)	0.0035
Symptom	EDS	-12.5 (1.758)	-17.7 (1.843)	-5.24 (-9.58, -0.90)	0.0181
	TOTAL OSDI	-3.95 (0.892)	-3.65 (0.947)	0.30 (-1.90, 2.50)	0.7897
	VR_OSDI	-0.13 (0.044)	-0.15 (0.048)	-0.02 (-0.13, 0.09)	0.7317
	ODS	-0.41 (0.075)	-0.61 (0.074)	-0.20 (-0.38, -0.02)	0.0340

OPUS-2

	Parameters	Placebo (N = 350)	LIF 5.0% (N = 328)	Difference in LSM (95% CI)	P-value
Sign	ICSS	-0.74 (0.051)	-0.79 (0.051)	-0.05 (-0.18, 0.08)	0.4636
	Nasal CLGSS	-0.30 (0.043)	-0.27 (0.044)	0.03 (-0.08, 0.14)	0.6110
	STT	2.15 (0.302)	2.42 (0.319)	0.27 (-0.54, 1.09)	0.5091
	Total CSS	-1.56 (0.112)	-1.73 (0.112)	-0.18 (-0.47, 0.12)	0.2376
Symptom	EDS	-24.0 (1.588)	-37.7 (1.548)	-13.7 (-17.8, -9.62)	<.0001
	TOTAL OSDI	-8.37 (1.027)	-15.1 (0.984)	-6.75 (-9.37, -4.13)	<.0001
	VR_OSDI	-0.28 (0.051)	-0.61 (0.049)	-0.33 (-0.47, -0.20)	<.0001
	ODS	-0.61 (0.065)	-0.98 (0.061)	-0.38 (-0.54, -0.21)	<.0001
	EDisS	-17.8 (1.575)	-28.7 (1.467)	-11.0 (-14.9, -7.03)	<.0001

The MMRM model used an unstructured covariance matrix to account for correlated measurements within patient and included the fixed effects for treatment, visit, actual baseline values, strata, and the interaction terms of treatment by visit.

Reference ID: 3795926

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

/s/

SOLOMON CHEFO
07/22/2015

YAN WANG
07/22/2015
I concur.

TSAE YIN D LIN
07/22/2015

Statistics Filing Checklist for NDA - 208073

NDA Number:	208073
NDA Type:	Priority Review
Drug Name:	Xiidra (lifitegrast ophthalmic solution) 5.0 %
Indication:	Treatment of the signs and symptoms of dry eye disease
Applicant:	SHIRE DEVELOPMENT LLC
Stamp Date:	February 25, 2015
Reviewer:	Solomon Chefo

1. Brief Summary of Controlled Clinical Trial(s)

The submission contains four clinical studies; one Phase 2 efficacy and safety study, two phase 3 efficacy and safety study, and one Phase 3 safety study. Brief summary for the efficacy and safety studies are provided in Appendix 1.

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information from Review of the Protocol and the Study Report

Content Parameter	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	☑			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	☑			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			☑	
Appropriate references for novel statistical methodology (if present) are included.			☑	
Safety data organized to permit analyses across clinical trials in the NDA.	☑			
Investigation of effect of missing data and discontinued follow-up on statistical analyses as described by applicant appears adequate.	☑			

Reference ID: 3718312

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\cdsesub1\evsprod\nda208073
Dataset structure (e.g., SDTM or ADaM)	YES
Based on the analysis datasets, can results of the primary endpoint(s) be reproduced? (Yes or No)	YES [(a)]
List the dataset(s) that contains the primary endpoint(s)	Dataset name **adef.xpt** and primary efficacy variable **chg** is the primary efficacy variable**.**
Are there any concerns about site(s) that could lead to inspection? If so, list of site(s) that needs inspection and rationale	NA
Are the define files sufficiently detailed?	NO
Safety data are organized to permit analyses across clinical trials in the NDA.	YES

(a) We were able to produce the primary endpoint results; however, our results are slightly different from the applicant's result.

4. Filing Issues

Table 4: Initial overview of the NDA/BLA application for refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	☑			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	☑			• ISS datasets were included in the submission. • Complete study reports were available for individual studies.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		☑		
Data sets in EDR are accessible and conform to applicable guidance (e.g., existence of define.pdf file for data sets).	☑			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? <u>YES</u>

Based on our preliminary review, the NDA is fileable. However, issues are noted. We have the following review issue to be forwarded to the Applicant for the 74-day letter.

i) In the primary efficacy analysis for Study 1118-DRY-300 (OPUS-2), you stated that '*ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size*' was used to assess the treatment effect. However, in the SAS program you referred to in the clinical study report (i.e., **t-eff.sas**), a two sample t-test was used for treatment comparison. Please clarify and submit the right SAS code used to produce the primary efficacy result for this study.

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Appendix 1: Brief summary of Active-Control clinical trials

Study/Phase	**Study Design**	**Treatment (Sample Size)**	**Diagnosis (Population)**	**Primary Endpoint/ Analysis/Applicant results**
1118-KCS-100 / Efficacy & Safety Study Primary Study Objective To evaluate the efficacy of 3 different concentrations (0.1, 1.0, 5.0%) of the test product (lifitegrast) compared to placebo in the treatment of dry eye as assessed by *inferior corneal staining* (ICSS) measured without the use of controlled adverse environment (CAE). Comparisons were made during 12 weeks of treatment with twice daily dosing.	Phase 2, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel arm study. Visits on Days -14, 0, 14, 42, and 84. During the screening period (Day -14 to Day 0) all subjects received Placebo drop BID, and measurements were taken Pre- and Post-CAE	Lifitegrast 0.1% [N = 57], Lifitegrast 1.0% [N = 58], or Lifitegrast 5.0% [N = 58], or Placebo [N = 57] ophthalmic solution; single drop administered twice daily (BID) • All patients enrolled at 5 study sites in the United States	Subjects at least 18 years of age with: • Reported history of dry eye in both eyes • Corneal fluorescein staining score ≥2 (0–4 point Ora scale) in at least 1 eye pre-CAE at Days -14 and 0. • Conjunctival redness score ≥1 (0–4 point Ora scale) in at least 1 eye pre–CAE at Days -14 and 0	The primary endpoint of the study was inferior corneal staining score at Day 84. • ANCOVA model with the inferior corneal staining score at Day 84 as a response variable and with treatment, baseline score, and site as covariates was used as the primary efficacy analysis. • The applicant used Dunnett's test in the ANVOVA model to compare each concentration group of lifitegrast versus placebo: **None of the lifitegrast dose groups were statistically significant different from the Placebo group in inferior corneal staining score at Day 84**. • Unadjusted comparison in the mean change in ICSS between the proposed dose of Lifitegrast 5.0% (+0.05) versus Placebo (+0.40) was made using a 2-sample t-test, and a treatment difference was observed from Baseline to Day 84 (p=0.0209). The reviewer conducted similar analysis for the symptom variable based on VR_OSDI and based on VAS score for Dry Eye symptom, and none of the lifitegrast dose groups were statistically significant different from the Placebo group for both symptom variables (See Figure in Appendix 2).

Reference ID: 3718312

Study/Phase	Study Design	Treatment (Sample Size)	Diagnosis (Population)	Primary Endpoint/ Analysis/Applicant results
1118-KCS-200 (OPUS-1)/ Efficacy & Safety Study Primary Study Objective To evaluate the efficacy of lifitegrast compared to placebo in the treatment of dry eye as assessed by the co-primary endpoints of *inferior corneal fluorescein staining* (0-4 point Ora scale, ocular sign) and *visual-related function Ocular Surface Disease Index subscale (VR_OSDI)* score (0-4 point mean composite score; items 6-9 regarding reading, driving at night, use of computer, and watching television) of the Ocular Surface Disease Index® (each measured by mean change from baseline to Day 84.	Phase 3, multicenter, randomized, prospective, double–masked, placebo–controlled, parallel–arm. Randomization was stratified by active use of artificial tears. Visits on Days -14, 0, 14, 42, and 84. During the screening period (Day -14 to Day 0) all subjects received Placebo drop BID, and measurements were taken Pre- and Post-CAE	Lifitegrast 5.0% [N= 293] or Placebo [N = 295] ophthalmic solution; single drop BID (in the morning and just before bedtime in the evening) in both eyes • All patients enrolled at 13 study sites in the United States	Subjects at least 18 years of age with: • Reported history of dry eye in both eyes • Corneal fluorescein staining score of ≥2 in at least 1 region in at least 1 eye pre-CAE at Days -14 and 0. • Conjunctival redness score ≥1 in at least 1 eye pre–CAE at Days -14 and 0	The study included co-primary endpoints of: (i) inferior corneal fluorescein staining score and (ii) visual-related function Ocular Surface Disease Index subscale (VR_OSDI) score. • The mean change from baseline to Day 84 in inferior corneal fluorescein staining score and VR-OSDI score was compared between lifitegrast and placebo treatment groups using a 2-sample t-test based on the ITT Population with last observation carried forward. • The lifitegrast treatment group had a statistically significant mean decrease (improvement) from baseline to Day 84 in inferior corneal fluorescein staining score (-0.07) as compared to the placebo treatment group (+0.17) (p=0.0007). • The placebo and lifitegrast treatment groups had 0.12 and 0.11 mean decreases (improvements) in VR-OSDI score from baseline to Day 84, respectively. The difference between treatment groups was not statistically significant (p=0.7860). The reviewer conducted similar analysis for the symptom variable based on VAS score for Dry Eye symptom. • The placebo and lifitegrast treatment groups had 11.2 and 15.2 mean decreases (improvements) in VAS score from baseline to Day 84, respectively. The difference between treatment groups was not statistically significant (p=0.1137). • When the analysis was restricted in patients with baseline eye dryness score (VAS score

Reference ID: 3718312

Study/Phase	Study Design	Treatment (Sample Size)	Diagnosis (Population)	Primary Endpoint/ Analysis/Applicant results
				≥ 40) and with documented history of artificial tear use at baseline (as in Study **1118-DRY-300** below), the placebo and lifitegrast treatment groups had 22.1 and 35.4 mean decreases (improvements) in VAS score from baseline to Day 84, respectively. The difference between treatment groups appeared to be statistically significant (p=0.0178).
1118-DRY-300 (OPUS-2)/ Efficacy & Safety Primary Study Objective To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye in **subjects currently using artificial tears** as assessed by the co-primary endpoints of: • Sign – inferior corneal fluorescein staining measured by mean change from baseline to Day 84 in the designated **study eye** • Symptom – eye dryness score (0–100 point visual analogue scale, **both eyes**) measured by mean change from baseline to Day 84.	Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Visits on Days -14, 0, 14, 42, and 84 Randomization was stratified by Day 0 inferior corneal fluorescein staining score and eye dryness score in the study eye as follows: i) inferior corneal staining score ≤1.5 in the study eye and eye dryness score <60 ii) inferior corneal staining score ≤1.5 in the study eye and eye dryness score ≥60	Lifitegrast 5.0% [N= 358] or Placebo [N = 360] ophthalmic solution; single drop BID (in the morning and just before bedtime in the evening) in both eyes All patients enrolled at 30 study sites in the United States	Subjects at least 18 years of age with: • Reported history of dry eye in both eyes • Corneal fluorescein staining score ≥2 in at least 1 region in at least 1 eye pre-CAE at Days -14 and 0. • Conjunctival redness score ≥1 in at least 1 eye pre–CAE at Days -14 and 0 • Eye dryness score ≥40 at Days -14 and 0. • Use of non-prescription artificial tear substitutes for dry eye within 30 days prior to Day -14, but willing to suspend use of artificial tears from 72 hours prior to Day -14 until study completion	The study included co-primary endpoints: (i) inferior corneal fluorescein staining score and (ii) eye dryness score (0–100 point visual analogue scale (VAS) in both eyes). • In the applicant primary analysis, the mean change from baseline to Day 84 in inferior corneal fluorescein staining score and in eye dryness score were compared between lifitegrast and placebo treatment groups using ANCOVA based on the ITT population with last observation carried forward. The ANCOVA model included treatment, strata, and the interaction between treatment and strata. • Based on the applicant analysis, the lifitegrast group did not have a statistically significant mean improvement in inferior corneal fluorescein staining score from baseline to Day 84 (-0.73) as compared to the placebo group (-0.71; p=0.6186). • The lifitegrast group had a statistically significant mean improvement from baseline to Day 84 in eye dryness score (-35.30) as compared to the placebo group (-22.75) (**p<0.0001**).

Reference ID: 3718312

Study/Phase	Study Design	Treatment (Sample Size)	Diagnosis (Population)	Primary Endpoint/ Analysis/Applicant results
	iii) inferior corneal staining score >1.5 in the study eye and eye dryness score <60 iv) inferior corneal staining score >1.5 in the study eye and eye dryness score ≥60			The reviewer conducted similar analysis for the symptom variable based on VR_OSDI score. • The placebo and lifitegrast treatment groups had 0.25 and 0.58 mean decreases (improvements) in VR_OSDI score from baseline to Day 84, respectively. The difference between treatment groups was statistically significant (**p<0.0001**).

Reference ID: 3718312

Study 1118-KCS-100 – Phase 2 Efficacy and Safety Study

Table 3: Subject Disposition (ITT Population)

	0.1% LIF N=57 n (%)	1.0% LIF N=57 n (%)	5.0% LIF N=58 n (%)	Placebo N=58 n (%)	Total N=230 n (%)
Number of screened subjects					545
Number of randomized subjects (ITT Population)	57 (100.0)	57 (100.0)	58 (100.0)	58 (100.0)	230 (100.0)
Safety Population	57 (100.0)	57 (100.0)	58 (100.0)	58 (100.0)	230 (100.0)
Per-protocol Population	49 (86.0)	47 (82.5)	44 (75.9)	46 (79.3)	186 (80.9)
Subjects who completed the study	54 (94.7)	51 (89.5)	48 (82.8)	48 (82.8)	201 (87.4)
Subjects discontinued from the study	3 (5.3)	6 (10.5)	10 (17.2)	10 (17.2)	29 (12.6)
Reason for withdrawal					
Adverse event	2 (3.5)	2 (3.5)	6 (10.3)	1 (1.7)	11 (4.8)
Death	0	1 (1.8)	0	0	1 (0.4)
Lost to follow-up	0	0	1 (1.7)	2 (3.4)	3 (1.3)
Non-compliance	0	2 (3.5)	1 (1.7)	1 (1.7)	4 (1.7)
Other	1 (1.8)	1 (1.8)	2 (3.4)	6 (10.3)	10 (4.3)

ITT=intent-to-treat; LIF=lifitegrast
Source: Section 14, Table 14.1.1 and Table 14.1.3

Table 4: Subject Demographics (ITT Population)

	0.1% LIF N=57	1.0% LIF N=57	5.0% LIF N=58	Placebo N=58	Total N=230
Age (years)					
Mean (SD)	63.14 (13.100)	63.63 (11.883)	62.26 (12.220)	60.38 (12.930)	62.34 (12.523)
Minimum, maximum	26.0, 89.0	35.0, 91.0	31.0, 85.0	26.0, 89.0	26.0, 91.0
≥50 years, n	51	50	51	47	199
Sex, n (%)					
Female	47 (82.5)	40 (70.2)	47 (81.0)	45 (77.6)	179 (77.8)
Male	10 (17.5)	17 (29.8)	11 (19.0)	13 (22.4)	51 (22.2)
Ethnicity, n (%)					
Not Hispanic or Latino	56 (98.2)	57 (100.0)	58 (100.0)	58 (100.0)	229 (99.6)
Hispanic or Latino	1 (1.8)	0	0	0	1 (0.4)
Race, n (%)					
White	53 (93.0)	53 (93.0)	53 (91.4)	54 (93.1)	213 (92.6)
Asian	2 (3.5)	2 (3.5)	3 (5.2)	1 (1.7)	8 (3.5)
Black or African American	1 (1.8)	1 (1.8)	2 (3.4)	3 (5.2)	7 (3.0)
American Indian or Alaska Native	1 (1.8)	0	0	0	1 (0.4)
Other	0	1 (1.8)	0	0	1 (0.4)
Iris color, n (%)					
Brown	46 (40.4)	46 (40.4)	36 (31.0)	42 (36.2)	170 (37.0)
Blue	34 (29.8)	44 (38.6)	42 (36.2)	40 (34.5)	160 (34.8)
Hazel	24 (21.1)	18 (15.8)	30 (25.9)	20 (17.2)	92 (20.0)
Green	10 (8.8)	4 (3.5)	6 (5.2)	12 (10.3)	32 (7.0)
Gray	0	2 (1.8)	2 (1.7)	2 (1.7)	6 (1.3)

ITT=intent-to-treat; LIF=lifitegrast; SD=standard deviation
Source: Section 14, Table 14.1.2

Reference ID: 3718312

Table 6: Inferior Corneal Fluorescein Staining Score (Ora Scale) at Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

	0.1% LIF N=57	1.0% LIF N=57	5.0% LIF N=58	Placebo N=58
Baseline (Day 0, Week 0, Visit 2)				
n	57	56	58	58
Mean (SD)	1.78 (0.473)	1.82 (0.508)	1.77 (0.515)	1.65 (0.513)
Day 84 (Week 12, Visit 5)				
n	57	55	54	55
Mean (SD)	2.03 (0.868)	1.92 (0.768)	1.83 (0.680)	2.05 (0.715)
Treatment effect (SE)[a]	0.06 (0.138)	0.20 (0.139)	0.27 (0.140)	
95% confidence interval	(-0.26, 0.39)	(-0.13, 0.53)	(-0.06, 0.60)	
p-value	0.9381	0.3585	0.1375	

[a] Analysis of covariance model with treatment, baseline, and site. P-value compared to placebo from Dunnett's test.
Note: Ora corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=occasional; 2=countable; 3=uncountable, but not confluent; 4=confluent.
Note: Results presented in this table are from the study eye only.
ITT=intent-to-treat; LIF=lifitegrast; LOCF=last observation carried forward; SD=standard deviation; SE=standard error
Source: Section 14, Table 14.2.1.1

See Appendix 2 for the mean change (95% CI) in Inferior Corneal Staining Score (ICSS), Vision Related Ocular Surface Disease Index (VR_OSDI), and Visual Analogue Scale (VAS) for eye dryness from baseline over time.

1118-KCS-200 (OPUS-1) – Phase 3 Efficacy and Safety Study

Table 3: Subject Disposition (All Randomized Subjects)

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

[a] Percentages based on randomized subjects.
[b] These subjects had a reason for study withdrawal of adverse event. An additional subject in the placebo treatment group was withdrawn from treatment, but not the study, due to an adverse event (refer to Appendix 16.2, Listing 7.6 and Listing 1.4.
ITT=intent-to-treat
Source: Section 14, Table 1.1.1 and Table 1.1.2

Reference ID: 3718312

Table 4: Subject Demographics (Safety Population)

	Placebo N=295	Lifitegrast N=293	Total N=588
Age, mean (SD)	61.1 (11.77)	60.2 (12.21)	60.6 (11.99)
Sex, n (%)			
Male	78 (26.4)	64 (21.8)	142 (24.1)
Female	217 (73.6)	229 (78.2)	446 (75.9)
Ethnicity, n (%)			
Hispanic or Latino	7 (2.4)	6 (2.0)	13 (2.2)
Not Hispanic or Latino	288 (97.6)	287 (98.0)	575 (97.8)
Race, n (%)			
American Indian or Alaskan Native	2 (0.7)	1 (0.3)	3 (0.5)
Asian	2 (0.7)	3 (1.0)	5 (0.9)
Black or African American	11 (3.7)	16 (5.5)	27 (4.6)
White	276 (93.6)	270 (92.2)	546 (92.9)
Other	4 (1.4)	3 (1.0)	7 (1.2)
Iris color (study eye), n (%)			
Black	0	3 (1.0)	3 (0.5)
Blue	98 (33.2)	105 (35.8)	203 (34.5)
Brown	96 (32.5)	113 (38.6)	209 (35.5)
Hazel	71 (24.1)	52 (17.7)	123 (20.9)
Green	27 (9.2)	18 (6.1)	45 (7.7)
Gray	2 (0.7)	1 (0.3)	3 (0.5)
Other	0	1 (0.3)	1 (0.2)

SD=standard deviation
Source: Section 14, Table 1.2.1

Table 7: Inferior Corneal Fluorescein Staining Score (ITT Population with LOCF)

	Placebo N=295	Lifitegrast N=293
Change from baseline to Day 84 (Visit 5), mean (SD)	0.17 (0.819)	-0.07 (0.868)
Treatment difference (95% CI)	0.24 (0.10, 0.38)	
t-test p-value (primary analysis)	0.0007	
Wilcoxon p-value	0.0006	

Note: Corneal staining scoring is as follows: 0=no staining/none; 1=occasional/trace; 2=countable/mild; 3=uncountable, but not confluent/moderate; 4=confluent/severe.
Note: Results presented in this table are from the study eye only.
CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation
Source: Section 14, Table 3.1.1.1

Table 8: Visual-related Function Ocular Surface Disease Index Subscale Score (ITT Population with LOCF)

	Placebo N=295	Lifitegrast N=293
Change from baseline to Day 84 (Visit 5), mean (SD)	-0.12 (0.762)	-0.11 (0.829)
Treatment difference (95% CI)	-0.02 (-0.15, 0.11)	
t-test p-value (primary analysis)	0.7860	
Wilcoxon p-value	0.9065	

Note: Higher Ocular Surface Disease Index scores indicate greater ocular impairment.
CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation
Source: Section 14, Table 3.1.1.2

See Appendix 2 for the mean change (95% CI) in ICSS, VR_OSDI, and VAS score from baseline over time.

Reference ID: 3718312

1118-DRY-300 (OPUS-2) – Phase 3 Efficacy and Safety Study

Table 3: Subject Disposition

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

[a] The total screening count of 1455 subjects includes 1450 unique subjects.

[b] Percentages based on Randomized Population.

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

ITT=intent-to-treat

Source: Section 14, Table 1.1.1 and Table 1.1.2

Reference ID: 3718312

Table 4: Subject Demographics (Randomized Population)

	Placebo N=360	Lifitegrast N=358	Total N=718
Age (years)			
Mean (SD)	58.9 (14.26)	58.7 (13.93)	58.8 (14.09)
≥65 years, n (%)	135 (37.5)	122 (34.1)	257 (35.8)
≥75 years, n (%)	42 (11.7)	39 (10.9)	81 (11.3)
Sex, n (%)			
Male	95 (26.4)	73 (20.4)	168 (23.4)
Female	265 (73.6)	285 (79.6)	550 (76.6)
Ethnicity, n (%)			
Hispanic or Latino	64 (17.8)	79 (22.1)	143 (19.9)
Not Hispanic or Latino	296 (82.2)	279 (77.9)	575 (80.1)
Race, n (%)			
American Indian or Alaskan Native	2 (0.6)	4 (1.1)	6 (0.8)
Asian	14 (3.9)	19 (5.3)	33 (4.6)
Black or African American	34 (9.4)	30 (8.4)	64 (8.9)
Native Hawaiian or other Pacific Islander	3 (0.8)	2 (0.6)	5 (0.7)
White	305 (84.7)	303 (84.6)	608 (84.7)
Other	2 (0.6)	0	2 (0.3)
Iris color (study eye), n (%)			
Black	0	1 (0.3)	1 (0.1)
Blue	86 (23.9)	80 (22.3)	166 (23.1)
Brown	189 (52.5)	193 (53.9)	382 (53.2)
Hazel	49 (13.6)	56 (15.6)	105 (14.6)
Green	35 (9.7)	27 (7.5)	62 (8.6)
Gray	1 (0.3)	1 (0.3)	2 (0.3)

SD=standard deviation
Source: Section 14. Table 1.2.1

Table 9: Inferior Corneal Fluorescein Staining Score – Mean Change from Baseline to Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

	Placebo N=360	Lifitegrast N=358
Baseline (Day 0, Week 0, Visit 2), mean (SD)	2.40 (0.722)	2.39 (0.763)
Change from baseline to Day 84 (Week 12, Visit 5), mean (SD)	-0.71 (0.943)	-0.73 (0.926)
Treatment Effect (SE) [a]	0.03 (0.067)	
95% CI for Treatment Effect	-0.10, 0.17	
p-value	0.6186	

[a] ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.
Note: Corneal fluorescein staining scoring is as follows with 0.5 increments: 0=no staining; 1=few/rare punctate lesions; 2=discrete and countable lesions; 3=lesions too numerous to count, but not coalescent; 4=coalescent.
Note: Results presented in this table are from the study eye only.
ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SE=standard error
Source: Section 14, Table 3.1.1.1

Reference ID: 3718312

Table 10: Eye Dryness Score (Visual Analogue Scale) – Mean Change from Baseline to Day 84 (Week 12, Visit 5) (ITT Population with LOCF)

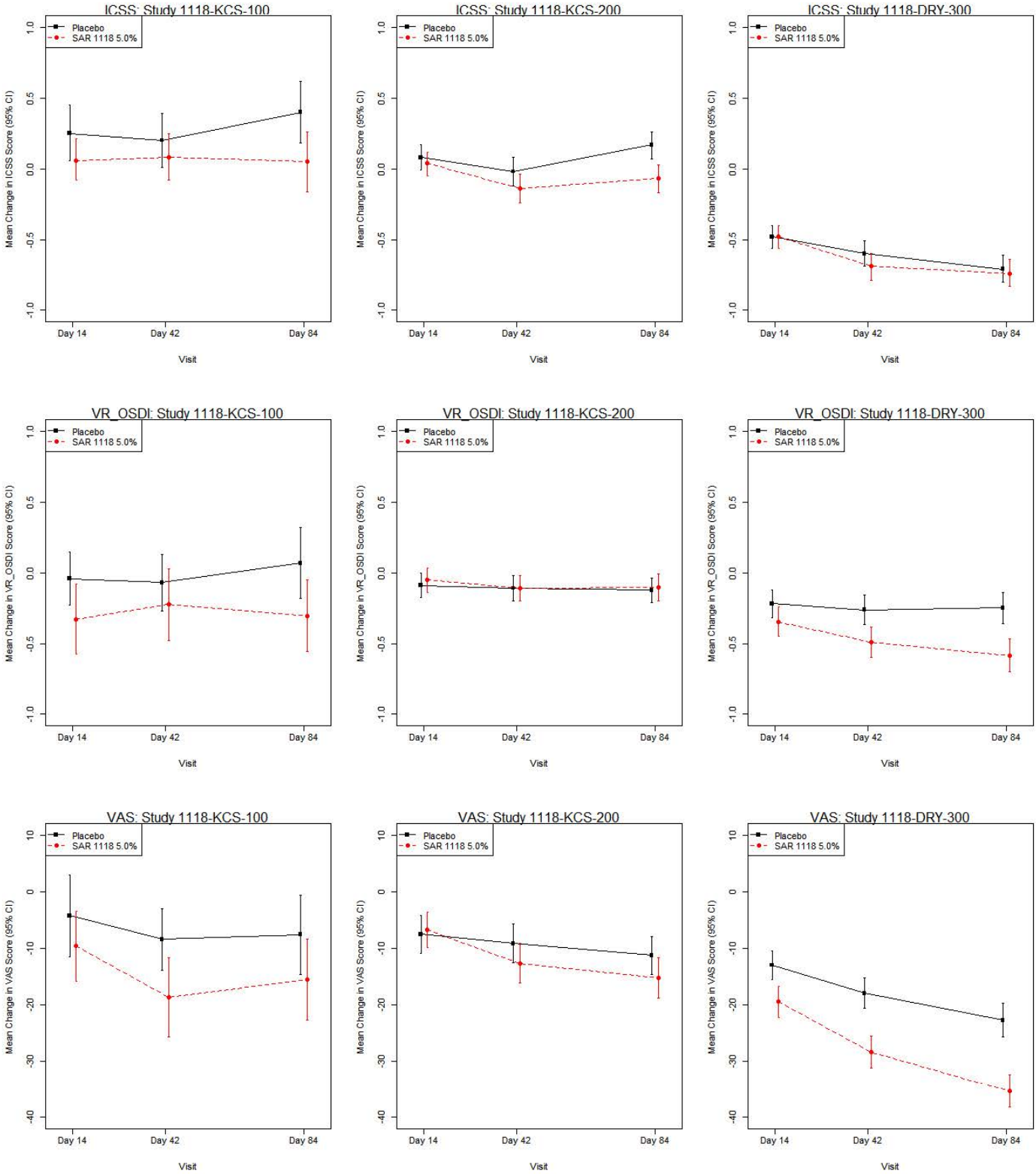
	Placebo N=360	Lifitegrast N=358
Baseline (Day 0, Week 0, Visit 2), mean (SD)	69.22 (16.761)	69.68 (16.954)
Change from baseline to Day 84 (Week 12, Visit 5), mean (SD)	-22.75 (28.600)	-35.30 (28.400)
Treatment Effect (SE) [a]	12.61 (2.085)	
95% CI for Treatment Effect	8.51, 16.70	
p-value	<0.0001	

[a] ANCOVA model of change with treatment, stratum, and treatment by stratum interaction; weights set to stratum size.
Note: Eye dryness score (VAS) uses 0-100 point scale (0=no discomfort; 100=maximal discomfort).
ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SE=standard error; VAS=visual analogue scale
Source: Section 14, Table 3.1.1.2

See Appendix 2 for the mean change (95% CI) in ICSS, VR_OSDI, and VAS score from baseline over time.

Reference ID: 3718312

Appendix 2:
Mean change (95% CI) in ICSS, VR_OSDI, and VAS score from baseline at each visit

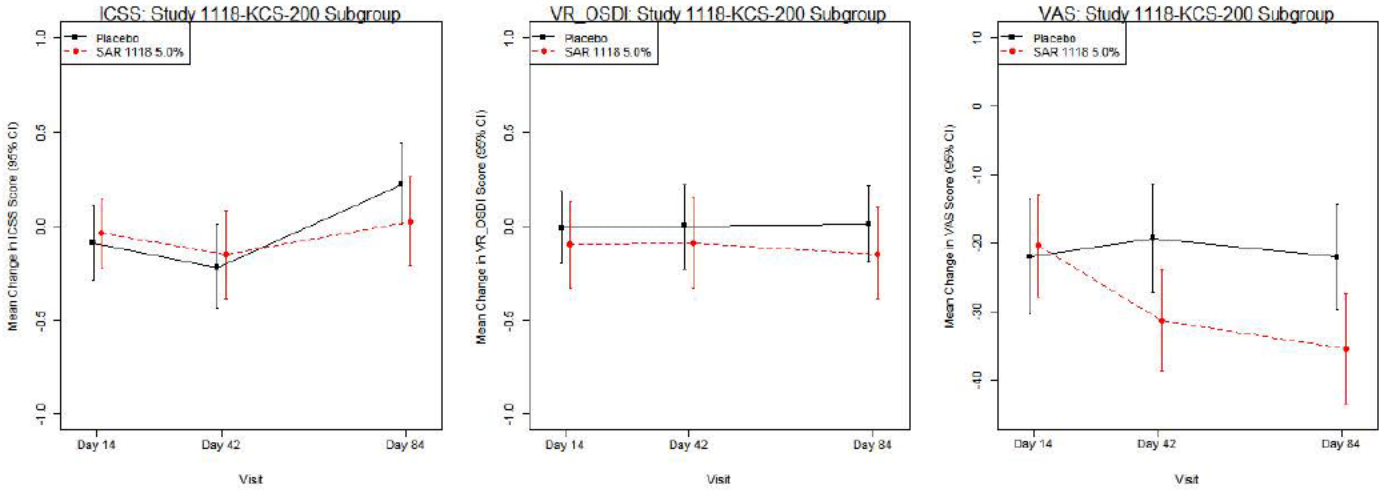


Source: Reviewer Analysis.

Reference ID: 3718312

Appendix 3:

Mean change (95% CI) in ICSS, VR_OSDI, and VAS score from baseline at each visit for the subgroup of patients with baseline eye dryness VAS score ≥ 40 and with documented history of artificial tear use at baseline (Study **1118-KCS-200)**



Reference ID: 3718312

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/s/

SOLOMON CHEFO
03/20/2015

YAN WANG
03/20/2015

STATISTICAL IND REVIEW AND EVALUATION

IND#:	NDA 208073
Serial #:	0017
Date of Submission:	11/18/2015
Name of Drug:	Lifitegrast ophthalmic solution, 5.0 %
Sponsor:	SHIRE DEVELOPMENT LLC
Indications:	Treatment of the signs and symptoms of dry eye disease
Documents Reviewed	Type A Meeting Briefing Package
Biometrics Reviewer:	Solomon Chefo
Clinical Reviewer	Rhea Lloyd
Project Manager:	Christina Marshall
EDR Location:	\\CDSESUB1\evsprod\NDA208073\0017

1. Introduction and Background

The sponsor (Shire, LLC) developed Lifitegrast ophthalmic solution, 5.0 % for the indication of treatment of the signs symptoms of dry eye disease (DED) (b) (4), and submitted the initial New Drug Application on 25 February 2015. In the NDA application, efficacy and safety support for the proposed indication was based on a Phase 2 dose-ranging study and two Phase 3 studies (OPUS-1 and OPUS-2). All studies were similar in design except that the Phase 2 and OPUS-1 studies enrolled subjects with mild-to-moderate symptoms while the OPUS-2 study enrolled subjects with moderate-to-severe symptoms. The statistical review for this NDA submission is posted in DARRTs (See entry 07/22/2015); the statistical review concluded that there is a lack of substantial evidence to support lifitegrast for the proposed indication of treatment of signs and symptoms of DED, and recommended that an adequate and well controlled study be conducted to provide additional efficacy data. Consequently, at the conclusion of the Agency's review of the lifitegrast NDA, the sponsor (Shire LLC) received a Complete Response Letter (CRL) from the Agency on 16 October 2015. In the CRL, the Agency requested that an additional clinical trial be conducted to provide substantial evidence of efficacy of the drug product in the intended patient population.

During the Pre-NDA meeting held on 15 May 2015, the need for an additional clinical trial was also discussed after preliminary results were presented during the meeting. Following the Pre-NDA meeting, the sponsor initiated OPUS-3 study, a Phase 3, multicenter, randomized, double-masked, and placebo controlled study comparing lifitegrast to placebo administered twice daily for 84 days (12 weeks). The sponsor indicated that OPUS- 3 was designed similar to OPUS-2 and included patients with dry eye with a recent history of artificial tear use within 30 days of study entry and an eye dryness score (EDS) ≥40 at baseline. Unlike OPUS-2 which evaluated a co-primary endpoint (sign and symptom), the primary endpoint in OPUS-3 was to evaluate the efficacy of lifitegrast compared to placebo in improvement of only symptoms of dry eye as measured by the mean change from Baseline to Day 84 in the EDS. Two key secondary endpoints of the mean change from Baseline to Day 42 and Baseline to Day 14 in the EDS were also assessed in OPUS-3 as key secondary endpoints.

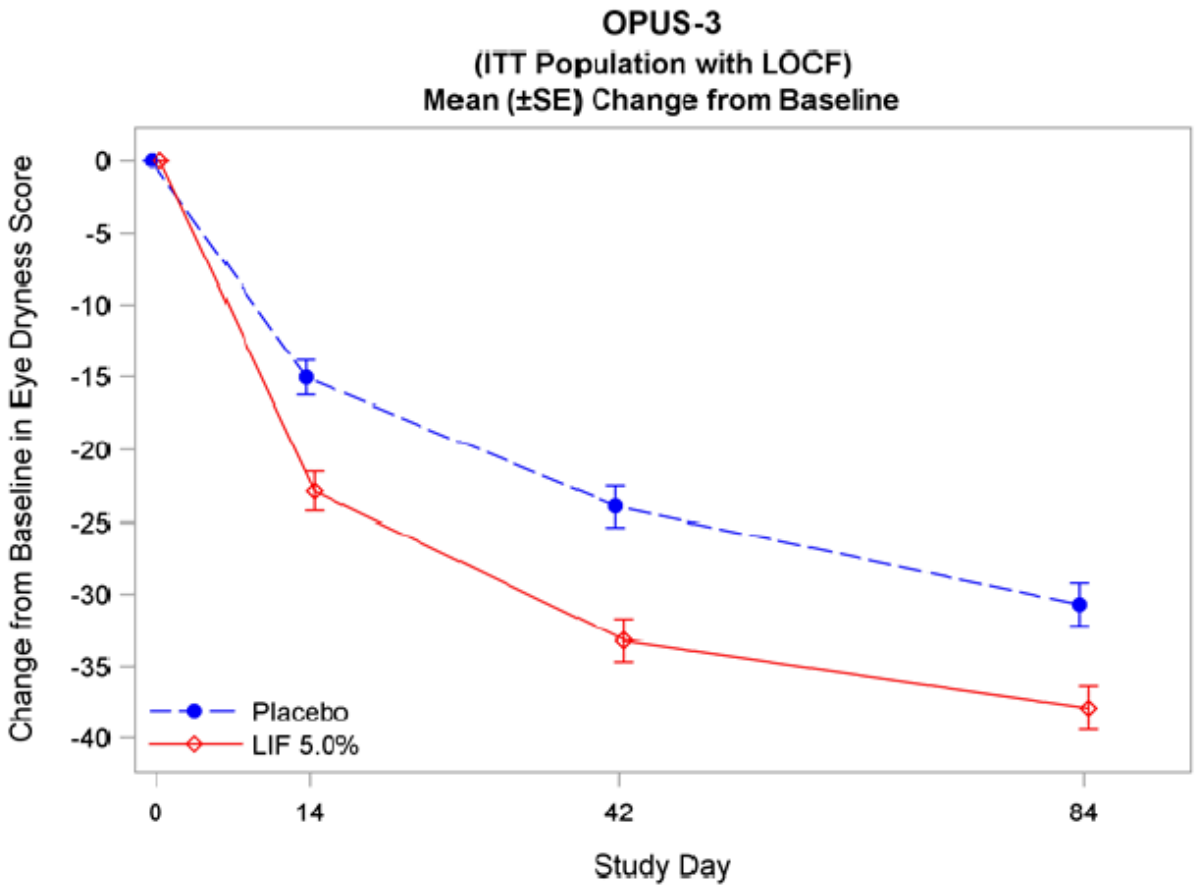
It should be noted that no efficacy endpoint was specified for **signs of dry eye** in the OPUS-3 study even though the study planned to collect all sign related data that were collected and analyzed in OPUS-1 as well as in OPUS-2 studies.

Reference ID: 3857868

In this submission, the sponsor requested an End of Review Conference Type A meeting with the Agency. The purpose of the meeting is to provide the Agency the resubmission application format and content intended to address the deficiencies listed in the CRL to support approval of lifitegrast for the proposed indication.

As part of the Type A meeting submission package, the sponsor presented topline data from OPUS-3 study that was available in November 2015. The sponsor's primary efficacy results showed that lifitegrast met the single primary endpoint for patient-reported symptoms of eye dryness (mean change in EDS from Baseline to Day 84 treatment difference of 7.16; (95% CI: 3.04, 11.28; p-value=0.0007). Further, the study met the key secondary endpoints (mean change in EDS from Baseline at Days 42 and Day 14 treatment differences of 9.32 (95% CI: 5.44, 13.20) and 7.85(95% CI: 4.33, 11.37), respectively, (p<0.0001).

Figure 3 Primary and Key Secondary Endpoints for OPUS-3



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2. Sponsor's questions and the reviewer's responses

Below is the list of sponsor's questions for discussion with the Agency, and the statistical reviewer response:

Question 1:

Shire seeks the Agency's agreement that the format and content of the planned resubmission application intended to address the deficiencies outlined in the Agency's CRL is sufficient to support its review?

Reviewer's Response:

We understand that the primary objective of OPUS-3 study was to evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo ***in improvement of symptoms of dry eye disease (DED),*** *but it is not clear to us from the study protocol as well as from the statistical analysis plan that the results for* ***the signs of DED*** *will be included in the clinical study report and in the integrated summary of efficacy.*

The Agency expects that the results for all the signs of DED variables - that were provided during the initial NDA submission - also be provided for the individual OPUS-3 study as well as for the integrated summary of efficacy. We otherwise agree with your planned format and content.

Question 2

Does the Agency consider that an Advisory Committee will be convened during the review of the resubmission application?

Reviewer's Response: Defer to the clinical team.

Clinical Team Response:

There are currently no plans to convene an Advisory Committee during the review of the resubmission application. However, a final decision regarding an Advisory Committee meeting will be made after the application is resubmitted.

Reference ID: 3857868

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/s/

SOLOMON CHEFO
12/09/2015

YAN WANG
12/09/2015