STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP606-304
Protocol Title:	A Phase 3, Multicenter, Randomized, Double-masked, and Placebo-controlled Study Evaluating the Efficacy and Safety of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye Disease and History of Recent Artificial Tear Use (OPUS-3)
Drug:	Lifitegrast ophthalmic solution
Sponsor:	Shire Development LLC and International Affiliates 725 Chesterbrook Boulevard Wayne, Pennsylvania 19087
Version No. and Date	Version 1.0 Date 21 January 2015

STATISTICAL ANALYSIS PLAN APPROVAL FORM

Drug: Lifitegrast	Protocol Number: SHP606-304
Protocol Name: OPUS-3	
Statistical Analysis Plan (SAP) Version Number: 1.0	Date: 21 January 2015

I confirm the final SAP for above noted study and approve the content for submission to the SAP approval team.

Study Biostatistician	[redacted] [redacted]
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	[redacted] 21 JAN 2015
	Sig[redacted]ture and Date (DD/MM/YYYY)

Statistical Analysis Plan Approval by SAP Approval Team Members
I approve the final SAP for the above study as it pertains to my area of expertise.
Note: An approver may delegate the review and approval of this document to an appropriately qualified and clearly identified (by name and title) designee.

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Note: If a Contract Research Organization executes the statistical and/or statistical programming activities, they will review the SAP, but not approve it.

Note: The study data manager will review the SAP, but not approve it.

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ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
BCVA	best corrected visual acuity
BID	bis in die, twice daily
CRO	Contract Research Organization
DED	dry eye disease
EDS	eye dryness score
[redacted]	[redacted]
ET	early termination
HEOR	Health Economics and Outcomes Research
ICS	inferior corneal staining
IRT	interactive response technology
ITT	intent-to-treat
LASIK	laser-assisted in situ keratomileusis
LOCF	last observation carried forward
LogMAR	minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
OD	oculus dexter, right eye
ODS	ocular discomfort score
OU	oculus uterque, both eyes or each eye
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SOC	system organ class
STT	Schirmer Tear Test
TEAE	treatment-emergent adverse event
US	United States
VAS	visual analogue scale

WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety, and Health Economics and Outcomes Research (HEOR) data as described in the final study protocol version 2.0 dated 22 Dec 2014. Specifications for tables, figures, and listings are contained in a separate document.

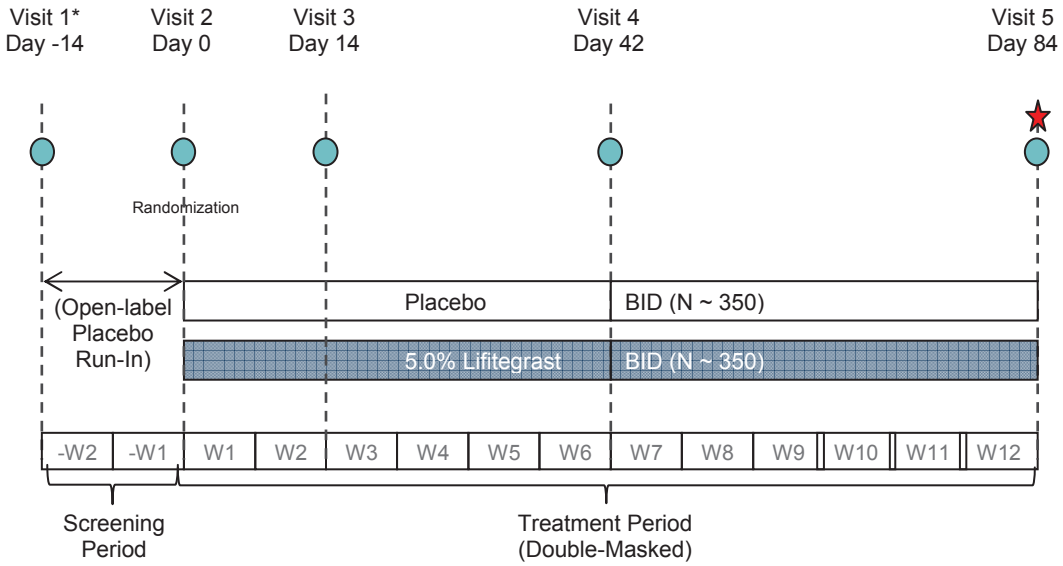
2. STUDY DESIGN

2.1 General Study Design

This is a Phase 3, randomized, multicenter, double-masked, placebo-controlled, parallel arm study to evaluate the efficacy and safety of a 5.0% concentration of lifitegrast ophthalmic solution administered twice daily in each eye for 12 weeks in subjects with dry eye disease (DED) recently using artificial tears.

There are 5 visits in this study; a screening visit (Visit 1, Day -14 ± 3 OR up to +84 depending on the washout timeframes), a confirmatory screening visit (Visit 2, Day 0) and 3 visits in the treatment period (Visits 3-5).

Figure 1: Study Design Flow Chart



*Screening Period (Visit 1/Week -2); Days -14 to -1 (± 3, OR up to +84).

To be eligible for the study, subjects must have the following:

- history of DED in both eyes
- best corrected visual acuity (BCVA) of 0.7 logMAR or better in each eye (OU) at Visit 1
- corneal fluorescein staining score ≥ 2 (0-4 point scale) in at least 1 region in at least 1 eye at Visits 1 and 2
- conjunctival redness score ≥ 1 (0-4 point scale with allowance for 0.5 point increments) in at least 1 eye at Visits 1 and 2
- eye dryness score (EDS) ≥ 40 (0-100 point visual analogue scale [VAS], both eyes [OU]) at Visits 1 and 2

- inferior corneal staining (ICS) score of ≥ 0.5 point (0–4 point scale with allowance for 0.5 point increments) in at least 1 eye at Visits 1 and 2
- Schirmer Tear Test (STT) without anesthesia ≥ 1 and ≤ 10 mm in at least 1 eye at Visits 1 and 2

The eye that meets these criteria will be the designated study eye. If both eyes meet the criteria above, the eye with the greater ICS score at Visit 2 will be designated as the study eye. If both eyes have equal ICS, then the eye with the lowest STT value at Visit 2 will be designated as the study eye. If both eyes have equal ICS and STT scores at Visit 2, the right eye (OD) will be designated as the study eye.

Subjects who sign the informed consent and meet the eligibility criteria at the end of the screening visit will enter the 2-week, Open-label, Placebo Run-In Screening Period to assess compliance with twice daily medication administration.

Subjects will then return to confirm eligibility at Visit 2. Endpoint measurements scheduled for Visit 2 will serve as baseline assessments. In the event that an assessment is missing at Visit 2, the last data collected prior to treatment exposure will be considered as the baseline value.

Subjects who continue to meet all eligibility criteria at Visit 2 will be randomized and evaluated for efficacy and safety at Weeks 2, 6, and 12 (Visit 3-5; Days 14, 42, and 84, respectively). Subjects who fail to meet the eligibility criteria at Visits 1 or 2 will be considered screen failures. Subjects cannot be rescreened once they have been designated as a screen failure. Subjects who discontinue the study will not be replaced.

A Schedule of Assessments is displayed in Table 1.

2.2 Randomization

The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to the investigational product allocated to the subject once eligibility has been determined.

Randomization will be centralized across study sites. Subjects will be randomly assigned to receive 5.0% lifitegrast ophthalmic solution or placebo solution based on a 1:1 ratio [lifitegrast (5.0%):placebo] within the randomization stratum using permuted blocks. The central randomization will ensure the specified 1:1 ratio [lifitegrast (5.0%):placebo] within each stratum.

Subjects will be randomized into 1 of the following strata:

- Baseline Visit (Visit 2) ICS score ≤1.5 in the study eye and EDS <60
- Baseline Visit (Visit 2) ICS score ≤1.5 in the study eye and EDS ≥60
- Baseline Visit (Visit 2) ICS score >1.5 in the study eye and EDS <60
- Baseline Visit (Visit 2) ICS score >1.5 in the study eye and EDS ≥60

These strata are designed such that approximately equal numbers of subjects are expected within each stratum. However, the number of subjects randomized in the study is not forced to be equal in each stratum.

2.3 Masking

This is a double-masked study. Study personnel, including sponsor staff, will be masked with regard to treatment assignments.

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor as soon as possible after the individual subject's treatment assignment has been unmasked. In the case of an emergency, there will be a process identified for unmasking to ensure adequate treatment of the subject.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code, are recorded in the interactive response technology (IRT) and source documents. Upon breaking the mask, the subject is withdrawn from the study, but should be followed for safety purposes as appropriate.

Any code-breaks that occur must be reported to the sponsor and contract research organization (CRO). Code-break access will be provided via the IRT to the investigator/designated person at the site and the CRO medical monitor for the study.

With the exception of such emergency code breaks, the mask for the study will be broken only after all subjects have completed or terminated from the study, data issues have been resolved, and the database has been locked.

2.4 Schedule of Assessments

Table 1: Schedule of Assessments

Procedure	**Screening Period [a] Visit 1 Week -2 Days -14 to -1 (± 3; OR up to +84 See Table 2 for Washout Timeframes)**		**Visit 2 Week -1 Day 0**			Days 1-13	**Visit 3[b] Week 2 Day 14 ± 3**	Days 15-41	**Visit 4[b] Week 6 Day 42 ± 3**	Days 43-83	**Visit 5[b] Week 12 Day 84 ± 7**	**ET**
	Pre-Washout	**Post-Washout**	**Pre-random-ization**	**Random-ization**	**Post-random-ization**							
Informed consent [a]	X											
Demographic data	X											
Height and weight (subject-reported)	X											
Medical history/medication history [c]	X	X										
Concomitant medication assessment and reporting	X	X	X	X	X		X		X		X	X
Inclusion/exclusion criteria	X	X	X									
Urine pregnancy test [d]	X		X								X	X
Subjective Measures												
VAS [e]		X	X				X		X		X	X
ODS		X	X				X		X		X	X
Drop comfort assessment [f]					X		X		X		X	
[redacted]												
Objective Measures												
BCVA [h]		X	X				X		X		X [h]	X [h]

Procedure	**Screening Period [a] Visit 1 Week -2 Days -14 to -1 (± 3; OR up to +84 See Table 2 for Washout Timeframes)**		**Visit 2 Week -1 Day 0**			Days 1-13	**Visit 3[b] Week 2 Day 14 ± 3**	Days 15-41	**Visit 4[b] Week 6 Day 42 ± 3**	Days 43-83	**Visit 5[b] Week 12 Day 84 ± 7**	**ET**
	Pre-Washout	**Post-Washout**	**Pre-random-ization**	**Random-ization**	**Post-random-ization**							
Slit lamp biomicroscopy [i]		X	X				X		X		X [i]	X [i]
Conjunctival redness score assessment		X	X				X		X		X	X
Corneal fluorescein staining score assessment		X	X				X		X		X	X
Conjunctival staining (lissamine green)		X	X				X		X		X	X
STT (without anesthesia)		X	X				X		X		X	X
Dilated fundoscopy [j]		X [j]									X [j]	X [j]
Investigational Product Treatment												
Open-label placebo administration at study site		X [k]	X [l]									
Open-label placebo dispensation		X										
Open-label placebo administration at home		X [k]										
Open-label placebo vial collection/drug accountability/compliance assessed [m]			X									
Randomization				X								
Investigational product					X [n]		X [o]		X [o]		X [p]	

Procedure	Screening Period [a] Visit 1 Week -2 Days -14 to -1 (± 3; OR up to +84 See Table 2 for Washout Timeframes)		Visit 2 Week -1 Day 0			Days 1-13	Visit 3[b] Week 2 Day 14 ± 3	Days 15-41	Visit 4[b] Week 6 Day 42 ± 3	Days 43-83	Visit 5[b] Week 12 Day 84 ± 7	ET
	Pre-Washout	Post-Washout	Pre-randomization	Randomization	Post-randomization							
administration at study site												
Investigational product dispensation					X		X		X			
Investigational product administration at home						X	X	X	X	X		
Investigational product collection/drug accountability/compliance assessed [m]							X		X		X	X
AE assessment and reporting [q]	X	X	X	X	X	X	X	X	X	X	X	X
Access IRT	X	X		X			X		X		X	X
Study exit											X	X

[a] Subjects must sign informed consent prior to performing any study-related procedures. A washout period may be required to discontinue any prohibited medication or treatments. A subject should not be instructed to discontinue use of any medication or treatment to participate in this study until after informed consent has been obtained. Screening assessments may take place across several days to allow an appropriate time frame in which to complete all procedures and confirm study eligibility, but placebo run-in should not be dispensed until washout and all screening assessments required to confirm initial eligibility are complete. Subjects must be administrated placebo run-in for a minimum of 11 consecutive days immediately prior to Visit 2. Extensions to the screening window to accommodate washout timeframes from prohibited medications or treatments are not permitted beyond 98 days (see Table 2); some screening assessments may need to be repeated after washout.

[b] Every effort should be made to schedule visits on the designated study days; however, after baseline, visits will have a ±3 day visit window to allow for weekends and slight variations in subject schedules. Visits should be calculated from baseline and not the prior visit.

[c] All ocular medical history and ocular medications/treatments used to treat DED at any time should be recorded. Non-ocular medical history within 1 year of screening should be recorded. Non-ocular medications/treatments and ocular medications/treatments used for conditions other than DED within 60 days

Procedure	Screening Period [a] Visit 1 Week -2 Days -14 to -1 (± 3; OR up to +84 See Table 2 for Washout Timeframes)		Visit 2 Week -1 Day 0			Days 1-13	Visit 3[b] Week 2 Day 14 ± 3	Days 15-41	Visit 4[b] Week 6 Day 42 ± 3	Days 43-83	Visit 5[b] Week 12 Day 84 ± 7	ET
	Pre-Washout	Post-Washout	Pre-randomization	Randomization	Post-randomization							

prior to screening should be recorded.

[d] For all females.

[e] On visits when the VAS is completed, it should be completed prior to any other ophthalmologic test or assessment.

[f] Drop comfort assessments will be obtained for each eye immediately, 1, 2, and 3 minutes following instillation of the investigational product at the site by trained study personnel. If the score is not ≤3 at minute 3, the drop comfort should be repeated at minutes 5, 10, and 15 until the score is ≤3. If the score is >3 at minute 15, it should be recorded as an AE.

[redacted]

[h] A BCVA assessment will be measured prior to open-label placebo or randomized investigational product administration at all visits. At Visit 5, a second BCVA assessment will be measured after the final dose of investigational product is administered by site personnel. In the case where a subject may be determined to be an ET after dosing, this procedure should be performed.

[i] A slit lamp examination will be performed prior to open-label placebo or randomized investigational product administration at all visits. At Visit 5, a second slit lamp examination will be performed after the final dose of investigational product is administered by site personnel. In the case where a subject may be determined to be an ET after dosing, this procedure should be performed.

[j] Dilated fundoscopy should be performed at the end of the visit after other ophthalmic procedures/assessments have been completed, but prior to administration of open-label placebo or randomized investigational product.

[k] At the Screening Visit (Visit 1), following washout if applicable, for training purposes, subjects will self-administer open-label placebo approximately 15 minutes following the last study assessment (except for the drop comfort assessments) under the supervision of trained study personnel. Only 1 dose of open-label placebo will be administered on the day of Visit 1. Subjects will be instructed not to administer a second dose that day and to begin dosing the following morning. Subjects must be administrated placebo run-in for a minimum of 11 consecutive days immediately prior to Visit 2.

[l] At the Baseline Visit (Visit 2), trained site personnel will administer the open-label placebo approximately 15 minutes following the last screening study assessment. Subjects will be instructed not to administer a dose of open-label placebo at home prior to the visit. Subjects having a positive response and who continue to meet all other eligibility criteria will be randomized.

[m] Returned open-label placebo/investigational product must be reviewed and assessed for compliance and confirmation that all ampules are returned prior to dispensation of additional investigational product. Compliance issues must be discussed with subjects. Site personnel must confirm that subjects have not administered the morning dose prior to the office visit.

Procedure	**Screening Period [a] Visit 1 Week -2 Days -14 to -1 (± 3; OR up to +84 See Table 2 for Washout Timeframes)**		**Visit 2 Week -1 Day 0**			Days 1-13	**Visit 3[b] Week 2 Day 14 ± 3**	Days 15-41	**Visit 4[b] Week 6 Day 42 ± 3**	Days 43-83	**Visit 5[b] Week 12 Day 84 ± 7**	**ET**
	Pre-Washout	**Post-Washout**	**Pre-randomization**	**Randomization**	**Post-randomization**							

[n] For randomized subjects, trained site personnel will administer the first dose of randomized investigational product approximately 15 minutes following the instillation of the open-label placebo drops. Only 1 dose of randomized investigational product should be administered on the day of the Baseline Visit (Visit 2). Subjects will be instructed not to administer a second dose that day and to begin randomized dosing the following morning.

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

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

[q] Adverse events will be collected beginning from the signing of informed consent. The investigator should contact the medical monitor to discuss any ocular AEs that are persisting at Visit 5 or ET to agree to appropriate follow-up.

AE=adverse event; BCVA=best corrected visual acuity; DED=dry eye disease; ET=early termination; [redacted]; IRT=interactive response technology; ODS=ocular discomfort score; STT=Schirmer Tear Test; UNS=unscheduled visit; VAS=Visual Analogue Scale

2.5 Determination of Sample Size

The primary efficacy endpoint for this study is the change from baseline to Day 84 in EDS (0-100 point VAS) (details in Section 10).

A sample size of 350 subjects per treatment group (total 700) will ensure more than 90% power (95%) to detect a difference of 10.0 units (with standard deviation of 36.0) in mean change from baseline to Day 84 in EDS between lifitegrast and placebo at a 2-sided 5% type I error.

Additionally, there are 2 key secondary endpoints, which are change from baseline to Day 42 and change from baseline to Day 14 in EDS.

The sample size of 350 subjects per treatment group will also ensure more than 85% power (87%) to detect a difference of 8.0 units (with standard deviation of 34.0) in mean change from baseline to Day 42 between the treatment groups and more than 80% power (81%) to detect a difference of 6.5 units (with standard deviation of 30.0) in mean change from baseline to Day 14 between the treatment groups.

It is expected that few if any subjects will be excluded from the primary efficacy analysis due to missing data given that missing efficacy assessments will be imputed by last observation carried forward (LOCF).

2.6 Multiplicity Adjustments for Type I Error Control

The primary (and key secondary) efficacy analyses will be testing for difference in the mean change from baseline to Day 84 (or Day 42 and Day 14 for key secondary) between lifitegrast and placebo. Each test will be a 2-sided test in which the null hypothesis is there is no difference (difference equal to zero) in the mean change between the 2 treatment groups versus the alternative that there is a non-zero difference (details in Section 10).

In order to maintain study-wide Type I error control at 2-sided 5% level, the hypothesis testing for the primary and 2 key secondary efficacy endpoints will be done sequentially.

If the null hypothesis for the primary efficacy endpoint is rejected at 2-sided 5% level, then the first key secondary efficacy endpoint of change from baseline to Day 42 in EDS will be tested at 2-sided 5% level. If the null hypothesis for the first key secondary efficacy endpoint is rejected, then the second key secondary efficacy endpoint of change from baseline to Day 14 in EDS will be tested at 2-sided 5% level. A later test can only be reported as statistically significant if all earlier tests are also found significant.

3. OBJECTIVES

Primary

To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in improvement of symptoms of DED as measured by the mean change from baseline to Day 84 in EDS (0-100 point VAS, OU).

Key Secondary

To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in improvement of symptoms of DED as measured by:

- Mean change from baseline to Day 42 in EDS (0-100 point VAS, OU).
- Mean change from baseline to Day 14 in EDS (0-100 point VAS, OU).

Secondary

To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in improvement of symptoms of DED as measured by:

- Mean change from baseline to each visit (Day 14, 42, and 84) in the other 6 DED symptoms of the 7-item VAS (0-100 point).
- Mean change from baseline to each visit (Day 14, 42, and 84) in ocular discomfort score (ODS, 0-4-point scale) in the designated study eye.

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

4. SUBJECT POPULATION SETS

4.1 Screened Set

The Screened Set will consist of all subjects who have signed informed consent.

4.2 Randomized Population

The Randomized Population includes all subjects in the Screened Set for whom a randomization number has been assigned.

4.3 Safety Population

The Safety Population includes all randomized subjects who receive at least 1 dose of randomized investigational product.

4.4 ITT Population

The Intent-To-Treat (ITT) Population includes all subjects who receive at least 1 dose of randomized investigational product.

Analyses conducted using the ITT Population and Randomized Population will be based upon the treatment assigned while analyses conducted using the Safety Population will be based upon the treatment received.

5. SUBJECT DISPOSITION

The number of subjects included in each subject set (ie., Screened, Randomized, Safety, and ITT) will be summarized by randomized treatment group and overall, except for the Screened Set, which will be summarized for all subjects only.

Screen failures (ie., subjects who were screened but not randomized) with the associated reasons will be presented in a listing for the Screened Set.

The number and percentage of subjects who completed the study or withdrew from the study will be presented for each treatment group and for all subjects. For the subjects who prematurely withdrew from the study, the number and percentage of subjects for each primary reason of premature discontinuation will be presented by treatment group and overall. For subjects who withdrew from the study because of 1 or more protocol-defined withdrawal criteria, the number and percentage of subjects for each withdrawal criterion will be presented by treatment group and overall.

A listing of disposition will be provided for all subjects.

6. PROTOCOL VIOLATIONS

Protocol violations will be listed and summarized for subjects in the Randomized Population for each treatment group by site and overall. Summary tables will be presented with the following categories:

- Subjects not meeting the entry inclusion/exclusion criteria
- Subjects with incorrect stratification during randomization
- Subjects who took a prohibited medication during the study treatment period or prior to the first open label placebo dose without the proper washout
- Subjects with non-compliance of investigational product (<80% or >120% compliance)

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Randomized Population.

Descriptive statistics will be provided for the following subject characteristics at baseline:

- Age as a continuous variable
- Age by age groups (<65 years, ≥65 years, <75 years, ≥75 years)
- Sex
- Ethnicity (non-Hispanic, Hispanic)
- Race (American Indian, Asian, Black, Native Hawaiian, White, Other)
- Iris color in study eye (Black, Blue, Brown, Hazel, Green, Gray, Other)

Ocular and non-ocular medical history will be descriptively summarized based on the system organ class (SOC) and coded terms (Medical Dictionary for Regulatory Activities [MedDRA] version 14.1) by treatment group and overall for the Safety Population. Data summaries will be sorted by the overall frequency of reporting within SOC.

A listing of ocular and non-ocular medical history will be provided for the Randomized Population.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational Product

The duration of exposure to open-label placebo and double-masked investigational product will be summarized (n, mean, standard deviation, standard error, minimum, median, and maximum) by treatment group and overall for the Safety Population.

The duration of exposure to open-label placebo run-in is the number of days from the first to last day of placebo received during run-in.

The duration of exposure to double-masked investigational product is the number of days from first to last day of double-masked investigational product taken during the double-masked treatment period.

The duration of exposure will be presented by subject. All drug accountability information will be also presented chronologically by subject.

8.2 Measurement of Treatment Compliance

Overall compliance will be summarized by treatment group and overall for the Safety Population. Descriptive statistics (n, mean, standard deviation, standard error, minimum, median, and maximum) of treatment compliance, and the number and percentage of subjects with overall compliance between 80%-120% will be presented.

Vials will be counted at each follow-up visit with respect to: number dispensed at last visit, number returned unused, number returned used, and number missing.

Compliance will be calculated as:

(total number of used vials returned, including the vials used for on-site administration) /
(2 × [number of days of double-masked treatment for all days between the first and last day of dosing + 1 for both the first and last day of dosing where only 1 dose is to be administered])

9. PRIOR AND CONCOMITANT MEDICATION

Prior medication is defined as any treatment/medication used for DED within the subject's lifetime prior to the date of consent (Screening Visit, Visit 1) and any treatment/medication used for other ocular or non-ocular indications received within 60 days prior to the date of consent.

Concomitant medication refers to all treatment/medication taken between the date of consent and the end of the study (Day 84), inclusive. This includes medication with a start date prior to the date of the first dose of randomized investigational product and continuing after the first dose of the investigational product. Any medication with a start date after the date of the last dose of investigational product will not be considered a concomitant medication.

Medications can be counted both as prior and concomitant as it applies to the above definition.

Prior and concomitant medications will be summarized based on anatomical therapeutic chemical (ATC) and generic name (WHO dictionary version 2012 MAR) by treatment group and overall for the Safety Population.

The number and percentage of subjects receiving each medication will be presented and data will be sorted by the overall frequency of recorded use.

A subject who used the same medication (same generic name) multiple times will only be counted once for that medication. A subject who used multiple medications under the same ATC category will only be counted once for the category.

Ocular and non-ocular medications will be summarized separately.

All prior and concomitant ocular and non-ocular medications will be listed.

10. EFFICACY ANALYSES

The primary, key secondary, and secondary efficacy analyses will be performed on the ITT Population and presented by treatment group.

Baseline for all efficacy analyses is defined as the value for the efficacy assessment at Visit 2. If assessment at Visit 2 is missing, the last data collected prior to treatment exposure will be used as the baseline value. If a subject has repeated assessments at Visit 2, before the start of randomized investigational product, then the results from the final assessment made prior to the start of the randomized investigational product will be used as baseline.

Missing post-baseline efficacy assessments will be imputed using LOCF from post-baseline values and all efficacy analyses will be performed using LOCF, unless stated otherwise. If a subject has no post-baseline efficacy assessment then no LOCF will be done for that efficacy assessment for the subject. The subject will not be included in the ITT population with LOCF analysis for that efficacy assessment.

Subjects assigned to the incorrect stratum during randomization will be analyzed using the stratification used for the randomization.

All statistical tests will be 2-sided hypothesis tests performed at the 5% alpha level of significance for main effects. All confidence intervals will be 95% confidence intervals, unless stated otherwise.

Multiplicity adjustments (see Section 2.6) will be done on the primary and key secondary efficacy endpoints testing.

Additionally, subgroup analyses will be performed on the primary and key secondary efficacy endpoints. The following subgroups will be used: randomization strata, age groups (<65, ≥65, <75, ≥75), sex, and race. Descriptive statistics (n, mean, sd) by treatment group and treatment difference with 95% confidence interval will be displayed for each subgroup.

10.1 Primary Efficacy Endpoint(s) and Analysis

The primary efficacy endpoint is defined as the change from baseline to Day 84 in EDS (0-100 point VAS, OU).

The null hypothesis to be tested is that there is no difference in the mean change from baseline to Day 84 in EDS between lifitegrast ophthalmic solution (5.0%) and placebo with the alternative of a non-zero difference between them.

The primary analysis will be performed using a stratified 2-sample t-test (ie., analysis of variance). The stratified two-sample t-test will be referred to as analysis of variance (ANOVA) in this document. The stratification factors used for randomization will be used for this analysis. The individual strata will contribute to the overall analysis proportionate to their size as suggested by Anello, et al (2005). The ANOVA model used to conduct the protocol specified primary treatment comparison will include treatment, strata, and the interaction between treatment and strata.

The treatment effects will be estimated from the ANOVA model as described below.

The analysis will reflect the stratification of randomization through the use of a cell means model. The cells will be formed by the 8 combinations of the 4 strata and 2 treatments. In the cell means approach, the following mean estimates and differences are calculated (Table 2: Stratum Level Estimators).

Table 2: Stratum Level Estimators

Strata		Treatment Group		
ICS Score	ED Score	Lifitegrast (5.0%)	Placebo	Difference
≤ 1.5	< 60	$\bar{x}_{11}$	$\bar{x}_{12}$	$d_1=\bar{x}_{11}-\bar{x}_{12}$
	≥ 60	$\bar{x}_{21}$	$\bar{x}_{22}$	$d_2=\bar{x}_{21}-\bar{x}_{22}$
> 1.5	< 60	$\bar{x}_{31}$	$\bar{x}_{32}$	$d_3=\bar{x}_{31}-\bar{x}_{32}$
	≥ 60	$\bar{x}_{41}$	$\bar{x}_{42}$	$d_4=\bar{x}_{41}-\bar{x}_{42}$

ICS=inferior corneal staining, ED=eye dryness

For the ij-th mean, there is a corresponding sample size (n_{ij}) and estimated SD s_{ij}. For combining the treatment differences over strata, the weight for the i-th stratum is $w_i=n_i/n$ where n_i is the total sample size for the i-th stratum ($n_i=n_{i1}+n_{i2}$, i=1, 2, 3, 4) and n is the sum of the n_i over the four strata. Refer to Anello, et al (2005) for a discussion of the issues associated with the analysis of stratified (multicenter) trials and Lin (1999) for a description of using the total sample size within each stratum as the weight to combine stratum-specific estimators. This estimated treatment effect will be approximately the same as the observed mean for each treatment group ignoring stratification.

The overall difference and variance for the overall difference will be calculated as shown below.

Overall treatment effect

$$d=\bar{x}_{.1}-\bar{x}_{.2}=\sum_{i=1}^{4} w_i[\bar{X}_{i1}-\bar{X}_{i2}]$$

Estimated variance overall treatment effect

$$s_d^2=\sum_{i=1}^{4} w_i^2 s_p^2\left[\frac{1}{n_{i1}}+\frac{1}{n_{i2}}\right]$$

The overall estimated variance, s_p^2, is the mean square error calculated as the pooled variance over the 8 cells formed by the combination of treatment and stratum (ie., mean square error taken from a simple cell means ANOVA).

Calculations for the ANOVA estimates (differences, standard errors and confidence intervals) will be performed using PROC MIXED in SAS via the LSMEANS statement with the OM option and weights proportionate to stratum sample size. The model will be the cell means model (means estimated by treatment within stratum).

The primary inference will be based on the p-values from the ANOVA model for the change from baseline to Day 84 in EDS.

The interaction between treatment and strata is included in the model to allow for inconsistency across strata to be examined. The study is not powered to detect the effect of interaction between treatment and strata.

10.1.1 Sensitivity Analysis for the Primary Efficacy Endpoint

Sensitivity analyses will be done on the primary efficacy endpoint using additional statistical methods, particularly, a non-parametric Wilcoxon rank sum test (LOCF) and mixed model for repeated measures ANOVA (no imputation).

The stratified rank-based test will consist of repeating the primary analysis (ANOVA model using LOCF) using the overall ranks (Wilcoxon) rather than the observed data.

The repeated measures analysis will model the outcome as a function of the randomization strata, treatment, visit, and interaction between treatment and visit. In this model, all the model terms will be treated as categorical covariates. All analysis visits (see Section 17.1) will be included in the model. An unstructured covariance matrix will be used for this analysis.

Least squares means will be estimated for each treatment group at each visit. The difference between the least squares mean of the treatment groups will be provided with confidence interval for the primary efficacy endpoint.

Subjects assigned to the incorrect stratum during randomization will be analyzed using 1) the stratification used for the randomization, and 2) the stratum that would have been the correct stratum based on the baseline characteristics of the subjects.

10.2 Key Secondary Efficacy Endpoint(s) and Analysis

The 2 key secondary efficacy endpoints are defined as the change from baseline to Day 42 in EDS (0-100 point VAS, OU) and change from baseline to Day 14 in EDS (0-100 point VAS, OU).

The 2 key secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint by the stratified 2-sample t-test using the ANOVA model. Multiplicity adjustments (see Section 2.6) will be done on the key secondary efficacy endpoints testing.

Sensitivity analyses will be done on the key secondary efficacy endpoints similar to the primary efficacy endpoint.

The sensitivity analysis using repeated measures model will include all analysis visits in the model. Least squares means will be estimated for each treatment group at each visit. The differences between the least squares means of the treatment groups will be provided with confidence intervals for the secondary efficacy endpoints.

10.3 Other Secondary Efficacy Endpoint(s) and Analysis

The secondary efficacy endpoints are defined as the change from baseline to Day 14, Day 42, and Day 84 in the following scores:

- Ocular discomfort score (0-4 point scale) in the study eye

- Items of the VAS (0-100 point scale, OU): burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, and pain.

These endpoints will be analyzed similarly as the primary efficacy endpoint by the stratified 2-sample t-test using the ANOVA model.

No multiplicity adjustment will be done on the secondary efficacy endpoints. Summary statistics including nominal p-values will be reported.

11. SAFETY ANALYSES

Safety data will be presented for the Safety Population by treatment group.

The safety data collected at the Baseline Visit (Visit 2) or the last data collected prior to treatment exposure will be used as the baseline value for safety analyses.

11.1 Adverse Events

Each adverse event (AE) will be coded into a preferred term (PT) using Version 14.1 of MedDRA and grouped by SOC. Each AE will be identified as pre-treatment AE or treatment-emergent adverse event (TEAE).

TEAEs are defined as AEs that started or worsened on or after the date of the first dose of the double-masked, randomized investigational product.

If the start date of an AE is partially or completely missing and it is impossible to determine whether it is a TEAE, the AE will be considered a TEAE.

TEAEs will be classified as ocular or non-ocular and presented separately under these categories. Summary tables will be shown for all TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation. Additionally, TEAEs will be summarized according to intensity and relationship to the investigational product.

If intensity is missing for a TEAE, an intensity of "Severe" will be assigned. If the relationship to investigational product is missing for a TEAE, a causality of "Related" will be assigned. The imputed values, if any, will be used for incidence summaries, while the actual values will be presented in data listings.

In summary tables, subjects will be counted once per PT and once per SOC, at the maximum recorded intensity or relationship, as appropriate. SOCs and PTs will be sorted by frequency, unless otherwise specified.

Listings of all TEAEs will be provided by subject.

Pre-treatment events (captured on the AE form with a date/time that is before the first dose of randomized treatment) will be listed by subject but not tabulated.

11.2 Other Safety Variables

The following safety measures will be descriptively summarized by treatment group at each measured time point:

- Corneal fluorescein staining scores for inferior, superior, central regions (0-4 point scale for each region), and total (0-12 point scale derived from the sum of the regions)
- Best corrected visual acuity (logMAR scoring)
- Slit lamp biomicroscopy assessment (normal, abnormal - not clinically significant, abnormal - clinically significant) for 6 anatomic anterior segment regions: cornea, conjunctiva, iris, anterior chamber, lens, and lid

- Dilated fundoscopy assessment (normal, abnormal - not clinically significant, abnormal - clinically significant) for 5 anatomic posterior segment regions: vitreous, retina, macula, choroid, and optic nerve
- Drop comfort score (0-10 point scale)
- Conjunctival lissamine green staining score for nasal, temporal regions (0-4 point scale for each region), and total (0-8 point scale derived from the sum of the regions)
- Conjunctival redness score (0-4 point scale)
- Schirmer Tear Test without anesthesia (mm/5 min)

Where the measure is repeated for each eye, results will be presented for each eye.

Pregnancy test results at each time point will be provided in a listing.

12. OTHER ANALYSES

12.1 Health-related Quality of Life Analyses

[redacted]

13. INTERIM ANALYSIS

This study will have a masked safety analysis (prior to the database lock) for the 4-month safety update after the NDA submission.

14. DATA MONITORING/REVIEW COMMITTEE

There is no data monitoring committee for this study.

15. COMPUTER METHODS

Statistical analyses will be performed using Version 9.1.3 (or newer) of SAS® (SAS Institute, Cary, NC 27513) on a suitably qualified environment.

16. CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

No changes to the analyses specified in the protocol.

17. DATA HANDLING CONVENTIONS

17.1 Study Visits and Windows

Assessments will be assigned to visits based upon the date the assessment took place regardless of the CRF page completed. Assessments will be mapped to visits as outlined in Table 3.

Should there be more than 1 assessment mapped into in a given study visit, the assessment closest to the planned visit will be used for analysis (referred to as analysis visit); if equally close, choose the last assessment.

Study day will be calculated as follows:

Study day = assessment date - first dosing date (Day 0 or baseline visit)

All visits will be shown in the listings.

Table 3: Visit Windows (Study Day Based)

Visit	Start of Window	End of Window
Screening – Visit 1	Informed consent signed	-1
Baseline – Visit 2 Pre-randomization	0	Time of randomization
Visit 2 Post-randomization	Time of Randomization	0
Day 14 – Visit 3	1	27
Day 42 – Visit 4	28	62
Day 84 – Visit 5	63	Last recorded data

17.2 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, standard error, minimum, and maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percent of subjects in each category.

Hypothesis testing will be performed using 2-sided tests at $\alpha = 0.05$ significance level. All p-values will be rounded to 4 decimal places. If a p-value is less than 0.0001 it will be displayed as "< 0.0001".

17.3 Derived Efficacy Endpoints

There are no derived efficacy endpoints for this study.

17.4 Repeated or Unscheduled Assessments of Safety Parameters

If a subject has repeated assessments before the start of randomized investigational product, then the results from the final assessment made prior to the start of randomized investigational product will be used as baseline. If end of study assessments are repeated or unscheduled, the last post-baseline assessment will be used as the end of study assessment for generating descriptive statistics.

17.5 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Population, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

17.6 Missing Date Information for Prior or Concomitant Medications

Incomplete (ie., partially missing) start date and/or stop date for prior or concomitant medications will not be imputed. If both start and stop dates are incomplete and unable to determine whether prior or concomitant, the medication will be considered as concomitant.

17.7 Missing Date Information for Adverse Events

Incomplete (ie., partially missing) start date and/or stop date for adverse events will not be imputed. If both start and stop dates are incomplete and unable to determine whether an AE is treatment-emergent, the AE will be considered a TEAE.

17.8 Missing Severity Assessment for Adverse Events

If the severity is missing for an AE, then a severity of “Severe” will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

17.9 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE, a causality of “Related” will be assigned. The imputed values for relationship to randomized investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

18. REFERENCES

Anello C, O'Neill RT, Dubey S 2005. Multicentre trials: a US regulatory perspective. *Stat Methods Med Res*; 14(3): 303-18.

[redacted]

Lin X 1999. An issue of statistical analysis in controlled multi-centre studies: How shall we weight the centres? *Statist Med*; 18(4): 365-73.

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