PROTOCOL: SHP606-304

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: SHP606, Lifitegrast ophthalmic solution

IND: 077885

EUDRACT NO.: Non-EUDRACT

SPONSOR:

Shire Development LLC and International Affiliates
725 Chesterbrook Boulevard, Wayne, PA 19087 USA

PROTOCOL HISTORY: Original Protocol: 29 Jul 2014, Version 1.0

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** 29 JUL 2014
[redacted] DMD, DO [redacted]	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP606-304.

Title: A Phase 3, Multicenter, Randomized, Double-masked, and Placebo-controlled Study Evaluating the Safety and Efficacy 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

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of an SAE, the investigator must fax or e-mail the Shire Clinical Trial Serious Adverse Event Form within 24 hours to the Shire Pharmacovigilance Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of the Shire Clinical Trial Serious Adverse Event Form must also be sent to the Shire medical monitor by fax or e-mail using the details below.

[redacted] OD, MPH, FAAO
[redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>during normal business hours (8am to 5pm local time per region</u>, the investigator must contact the Shire medical monitor:

[redacted] OD, MPH, FAAO
[redacted]

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact the Shire medical monitor:

[redacted] OD, MPH, FAAO
[redacted]

Mobile: [redacted]

Email: [redacted]

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ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
BCVA	best corrected visual acuity
CRF	case report form
CRO	contract research organization
DED	dry eye disease
EC	ethics committee
EDS	eye dryness score
[redacted]	[redacted]
ET	early termination
EU	European Union
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
LASIK	laser-assisted in situ keratomileusis
LOCF	last observation carried forward
LogMAR	minimum angle of resolution
SAE	serious adverse event
SD	standard deviation
STT	Schirmer Tear Test
TEAE	treatment-emergent adverse event
US	United States
VA	visual acuity
VAS	visual analogue scale

STUDY SYNOPSIS

Protocol number: SHP606-304	**Drug:** SHP606, Lifitegrast ophthalmic solution
Title of the study: 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	
Number of subjects (total and for each treatment arm): Approximately 1400 subjects will be screened to ensure approximately 350 subjects per treatment group (approximately 700 total) are randomized.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 30 sites in the US	
Study period (planned): Oct 2014 – Dec 2015	**Clinical phase:** 3

Objectives:

Primary

To evaluate the efficacy of lifitegrast ophthalmic solution (5.0%) compared to placebo in improvement of symptoms of dry eye disease (DED) as measured by the mean change from baseline to Day 84 in the eye dryness score (EDS, 0-100 point visual analogue scale [VAS]).

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

Secondary

1. 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 in the 6 additional items of the 7-item VAS (0-100 point).
   - Mean change from baseline to each visit in the designated study eye in the ocular discomfort score (0- to 4-point scale).
2. To evaluate the safety and tolerability of lifitegrast ophthalmic solution (5.0%) compared to placebo.

Rationale:

This study is being conducted to provide safety data and efficacy data demonstrating improvement in symptoms associated with DED following twice daily treatment with lifitegrast for 12 weeks.

Investigational product, dose, and mode of administration:

The 5.0% concentration of lifitegrast ophthalmic solution was selected based on results from pre-clinical, Phase 1 healthy volunteer, Phase 2 dose-ranging, and 3 Phase 3 studies in DED subjects. Placebo is required as a comparator to demonstrate efficacy. Investigational product will be supplied as a sterile, clear, colorless to pale yellow liquid solution in single use, 0.99mL low density polyethylene unit dose ampules with a fill volume of approximately 0.25mL.

Open-label placebo or randomized treatment will be administered to the ocular surface twice daily as a single drop in each eye administered upon awakening and just before bedtime. Open-label placebo will be administered during the Screening Period to assess the subject's ability to comply with a twice daily regimen.

During the Treatment Period, subjects will receive randomized, double-masked 5.0% lifitegrast ophthalmic solution or placebo.

Open-label placebo or randomized treatment will be administered at the study site on days of office visits. At Visit 1, for training purposes, subjects will self-administer open-label placebo under the supervision of trained study personnel. At Visits 2-5, investigational product will be administered by trained study personnel. All other doses of open-label placebo and investigational product will be self-administered. Subjects will be asked not to administer 1 of their doses on visit days. Only 1 dose will be administered on the days of Visits 1 and 5. On the day of Visit 2, the first dose will be open-label placebo and the subsequent dose will be the randomized treatment. Both will be administered at the study site.

Methodology:

This is a Phase 3, randomized, multicenter, double-masked, placebo controlled 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. Subjects must have a history of recent artificial tear use, defined as within 30 days but not during the 72 hours prior to the Screening Visit (Visit 1) to be eligible for the study.

Approximately 700 subjects will be randomized 1:1 (approximately 350 per treatment arm) to receive either lifitegrast ophthalmic solution (5.0%) or placebo. Randomization will be stratified by inferior corneal fluorescein staining score ($\leq$1.5 or >1.5) and EDS (<60 or $\geq$60) at the Baseline Visit (Visit 2). Approximately 1400 subjects will be screened to ensure that 700 subjects are randomized.

Subjects who sign informed consent will be screened (Visit 1). Subjects who meet eligibility criteria at the end of the Screening Visit (Visit 1) will enter the 2-week, Open-label, Placebo Run-In Screening Period to assess compliance with twice daily medication administration. Subjects will return for the Baseline Visit (Visit 2) to confirm eligibility. Subjects who continue to meet all eligibility criteria will be randomized and will be evaluated for efficacy and safety at Weeks 2, 6, and 12 (Visits 3-5). Subjects who fail to meet 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 will not be replaced.

Inclusion and exclusion criteria:

The subject will not be considered eligible for the study until all of the criteria below are confirmed.

Inclusion Criteria

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated (personally or via a legally authorized representative) informed consent to participate in the study.
3. At least 18 years of age at the time of screening.
4. Male, or non-pregnant (confirmed by negative urine pregnancy test), non-lactating female who agrees to comply with any applicable contraceptive requirements of the protocol, or females of non-childbearing potential.
5. As-needed or scheduled use of non-prescription (OTC) artificial tear substitute for symptoms of DED within 30 days prior to the Screening Visit (Visit 1) and willingness to suspend use of tear substitutes 72 hours prior to Visit 1 and for the duration of study participation.
6. Best corrected visual acuity of 0.7 logMAR or better (logMAR<0.7; Snellen equivalent score of 20/100 or better) in each eye at Visit 1.
7. Subject-reported history of DED in both eyes.
8. Corneal fluorescein staining score $\geq$2 (0-4 point scale) in at least 1 region in at least 1 eye at Visits 1 and 2.
9. Conjunctival redness score $\geq$1 (0-4 point scale with allowance for 0.5 point increments) in at least 1 eye at Visits 1 and 2.

10. Eye dryness score ≥40 (0-100 point VAS, both eyes) at Visits 1 and 2.
11. A positive response in at least 1 eye, defined as meeting ALL of the following criteria in the same eye at both Visits 1 and 2:
    - Inferior corneal fluorescein staining score ≥0.5 (0-4 point scale with allowance for 0.5 point increments)
    - Schirmer Tear Test (without anesthesia) ≥1 and ≤10mm

Exclusion Criteria

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

the study.

16. Use of the following medications (topical, topical ophthalmic, systemic and/or injectable) within the time associated washout restrictions below or during the study:
    - Topical cyclosporine: within 6 weeks prior to Visit 1
    - Any medication (oral or topical) known to cause ocular drying: within 30 days of the Screening Visit (Visit 1) unless the subject has been receiving a stable dose over the past 30 days with no change in dose anticipated during the study period.
    - Oral aspirin or aspirin-containing products: within 30 days of the Screening Visit (Visit 1) unless the subject has been receiving a stable dose over the past 30 days prior to Visit 1 with no change in dose anticipated during the study period.
    - Corticosteroids or mast cell stabilizers (including ocular): within 14 days prior to the Screening Visit (Visit 1).
    - Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to Visit 1 and during the study; antihistamines are not allowed at any time during the study.
    - Antihistamines (including ocular): within 72 hours prior to Visit 1 and throughout the subject's participation during the study.
    - All other topical ophthalmic preparations (including artificial tear substitutes): within 72 hours prior to Visit 1.
17. Unwilling to avoid wearing contact lenses during the study.
18. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any planned ocular surgical procedure during the study period.
19. History of yttrium aluminum garnet-laser posterior capsulotomy in past 6 months prior to Visit 1.
20. Non-compliance (<80% or >120%) with placebo regimen during the Run-in Period.
21. Missing or unaccounted for ampules during the Run-in Period.

Maximum duration of subject involvement in the study:

- Planned duration of Screening Period: 14 days (2 weeks)
- Planned duration of Enrollment Period: 253 days (~36 weeks or ~8 months)
- Planned duration of Treatment Period: 84 days (12 weeks)

Endpoints and statistical analysis:

Subject Populations

- **Screened Set** will consist of all subjects who have signed an informed consent.
- **Randomized Population**: The Randomized Population includes all subjects in the Screened Set for whom a randomization number has been assigned.
- **Safety Population**: The Safety Population includes all randomized subjects who receive at least 1 dose of randomized investigational product.
- **Intent-to-treat (ITT)**: The ITT Population includes all randomized subjects who receive at least 1 dose of randomized investigational product and have at least 1 post-baseline primary efficacy assessment.

Primary Efficacy Endpoint

The change from baseline (Visit 2) to Day 84 in EDS (1-100 point VAS).

Key Secondary Efficacy Endpoints

- The change from baseline (Visit 2) to Day 42 in EDS (1-100 point VAS).
- The change from baseline (Visit 2) to Day 14 in EDS (1-100 point VAS).

Secondary Efficacy Endpoints

- The change from baseline (Visit 2) to each visit in each of the 6 additional individual items of the 7-item VAS (0-100 point).
- The change from baseline (Visit 2) to each visit in the ocular discomfort score (0-4 point scale) in the designated study eye.

Safety Endpoints

- Treatment-emergent ocular and non-ocular adverse events (AEs)
- Best corrected visual acuity
- Slit lamp biomicroscopy
- Dilated fundoscopy
- Drop comfort assessment
- Corneal fluorescein staining
- Conjunctival staining (lissamine green)
- Conjunctival redness score
- Schirmer Tear Test
- Pregnancy test

Health Economics and Outcomes Research Endpoints

- [redacted]

Statistical Methodology for Primary Efficacy Endpoint

The primary analysis of the subjective efficacy endpoint of the mean change from baseline to Day 84 of the EDS will be performed using a 2-sample t-test from ANOVA model (containing treatment, randomization strata, and treatment by strata interaction) comparing lifitegrast to placebo in the ITT Population with last observation carried forward (LOCF).

Statistical Methodology for Key Secondary Efficacy Endpoints

The key secondary subjective efficacy endpoints of the mean change from baseline to Day 42 and to Day 14 of the EDS will be performed using a 2-sample t-test from ANOVA model (containing treatment, strata and treatment by strata interaction) comparing lifitegrast to placebo in the ITT Population with LOCF.

In order to maintain study-wide type I error control, the primary and the 2 key secondary efficacy endpoints will be tested sequentially. A later test can only be reported as significant if all earlier tests are also found significant.

Statistical Methodology for Safety Endpoints

All safety measures including best corrected visual acuity, slit lamp biomicroscopy, dilated fundoscopy, drop comfort, corneal fluorescein staining, and conjunctival staining (lissamine green) will be summarized descriptively by treatment at all time points.

The number and percentage of subjects with treatment-emergent adverse events (TEAEs) will be calculated by system organ class and preferred term and presented by treatment group. The ocular and non-ocular TEAEs will be presented separately.

Sample Size Justification

A sample size of 350 subjects per treatment group (total 700) will ensure more than 90% power 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 5.0% type I error.

The sample size of 350 subjects per treatment group will also ensure more than 85% power to detect a difference of 8.0 units (with standard deviation of 34) in mean change from baseline to Day 42 between the treatment groups and more than 80% power to detect a difference of 6.5 units (with standard deviation of 30) in mean change from baseline to Day 14 between the treatment groups.

It is expected that no subject will be excluded from the primary efficacy analysis due to missing data given that the primary analysis is based on LOCF of on-treatment assessment.

STUDY SCHEDULE(S)

Table 1: Schedule of Study Assessments

	Screening Period		**Visit 2 Week -1 Day 0**									
Procedure	**Visit 1 Week -2 Day -14[a] ± 3**	Days -13 to -1	**Pre-random-ization**	**Random-ization**	**Post-random-ization**	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 ± 3**	**ET**
Informed consent [a]	X											
Demographic data	X											
Height and weight (subject-reported)	X											
Medical history/medication history [c]	X											
Concomitant medication assessment and reporting			X				X		X		X	X
Inclusion/exclusion criteria	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	

Table 1: Schedule of Study Assessments

Procedure	Screening Period		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 ± 3	ET
	Visit 1 Week -2 Day -14[a] ± 3	Days -13 to -1	Pre-random-ization	Random-ization	Post-random-ization							
Objective Measures												
BCVA[h]	X		X				X		X		X[h]	X[h]
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										

Table 1: Schedule of Study Assessments

Procedure	Screening Period		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 ± 3	ET
	Visit 1 Week -2 Day -14[a] ± 3	Days -13 to -1	Pre-random-ization	Random-ization	Post-random-ization							
Open-label placebo vial collection/drug accountability/compliance assessed [m]			X									
Randomization				X								
Investigational product administration at study site					X [n]		X [o]		X [o]		X [p]	
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
Study exit											X	X

Table 1: Schedule of Study Assessments

Procedure	Screening Period: Visit 1 Week -2 Day -14[a] ± 3	Days -13 to -1	Visit 2 Week -1 Day 0: Pre-randomization	Randomization	Post-randomization	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 ± 3	ET

[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 washout of any medication or treatment for this study until after informed consent has been obtained. The Screening Visit (Visit 1) assessments may take place across several days to allow an appropriate timeframe for washout. No subjective measures, objective measures, or investigational product-related measures should be performed until the appropriate washout has been completed. Extensions to the screening window to accommodate washout timeframes will be discussed on a case by case basis with the medical monitor and some screening assessments may need to be repeated.

[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 prior to screening should be recorded.

[d] For women only.

[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.

[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.

[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), 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.

Table 1: Schedule of Study Assessments

Procedure	Screening Period: Visit 1 Week -2 Day -14[a] ± 3	Screening Period: Days -13 to -1	Visit 2 Week -1 Day 0: Pre-randomization	Visit 2 Week -1 Day 0: Randomization	Visit 2 Week -1 Day 0: Post-randomization	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 ± 3	ET

[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.

[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 within 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

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Dry eye disease is a common and challenging problem for both clinicians and patients. Current treatments include artificial tears, punctal plugs, and cyclosporine. While cyclosporine is the only approved pharmacologic agent in DED, it is indicated for increasing tear production and is not indicated for the treatment of symptoms. Moreover, it is an immunosuppressant, has a long onset of action (24 weeks), and is associated with reduced tolerance due to burning sensations (RESTASIS® Package Insert [2013]). Despite the increasing understanding of the chronic inflammatory nature of ocular surface disease over the past 2 decades, there is an unmet need for pharmacologic agents approved to treat the symptoms associated with DED, the most common complaint of DED patients.

1.2 Product Background and Clinical Information

Lifitegrast ophthalmic solution 5.0% (hereafter referred to as lifitegrast) represents a new approach towards treating ocular surface inflammation that selectively targets a unique T-cell surface adhesion molecule, is not an immunosuppressant, and provides anti-inflammatory properties not available in OTC artificial tears.

To date, 1 Phase 2 and 2 Phase 3 efficacy studies have been conducted with lifitegrast in patients with DED. In these studies, lifitegrast has demonstrated improvement in signs of DED as measured by inferior corneal fluorescein staining and symptoms of DED as measured by EDS. In addition, a Phase 3, 52-week, double-masked, safety study has been completed demonstrating that lifitegrast appears to be safe and well-tolerated.

Always refer to the latest version of the SHP606 Investigator's Brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy, and safety of SHP606.

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This study is being conducted to provide safety data and efficacy data demonstrating improvement in symptoms associated with DED following twice daily treatment with lifitegrast for 12 weeks.

2.2 Study Objectives

2.2.1 Primary Objective

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 the EDS (0-100 point VAS).

2.2.2 Key Secondary Objective

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

2.2.3 Secondary Objectives

1. 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 in the 6 additional items of the 7-item VAS (0-100 point scale).
   - Mean change from baseline to each visit in the designated study eye in the ocular discomfort score (0-4 point scale).
2. To evaluate the safety and tolerability of lifitegrast ophthalmic solution (5.0%) compared to placebo.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

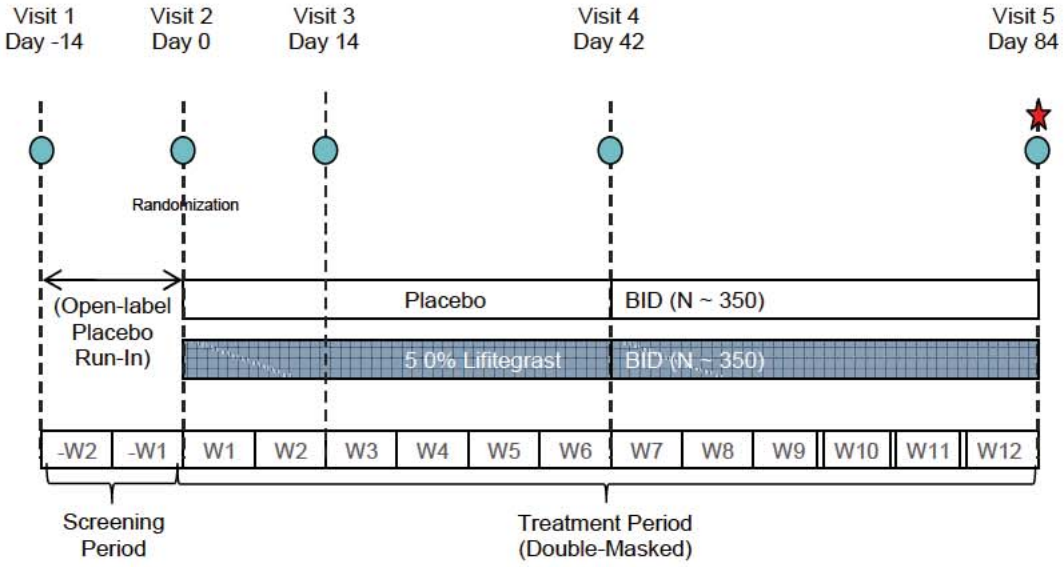
This is a Phase 3, randomized, multicenter, double-masked, placebo-controlled study to evaluate the efficacy and safety of a 5.0% concentration of lifitegrast ophthalmic solution administered twice daily in each eye for 12 weeks. The study will be conducted in adult male and female subjects with DED and a history of artificial tear use within 30 days of screening. Subjects must have a history of recent artificial tear use, defined as within 30 days but not during the 72 hours prior to the Screening Visit (Visit 1) to be eligible for the study.

Approximately 700 subjects will be randomized 1:1 (approximately 350 per treatment arm) to receive either lifitegrast ophthalmic solution (5.0%) or placebo. Randomization will be

stratified by inferior corneal fluorescein staining score (≤1.5 or >1.5) and EDS (<60 or ≥60) at baseline. Approximately 1400 subjects will be screened to ensure 700 randomized subjects.

Subjects who sign informed consent will be screened (Screening Visit [Visit 1]). Subjects who meet eligibility criteria at the end of the Screening Visit (Visit 1) will enter a 2-week Screening Period, during which all subjects will receive a standard regimen of open-label placebo to assess compliance with twice daily medication administration. Subjects will return for the Baseline Visit (Visit 2) to confirm eligibility. Subjects who continue to meet all eligibility criteria will be randomized and will be evaluated for efficacy and safety at Weeks 2, 6, and 12 (Visits 3-5). Subjects who fail to meet eligibility criteria at Visits 1 or 2 will be considered screen failures.

Figure 1: Study Design Flow Chart



3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 14 weeks (a 2-week screening period followed by a 12-week treatment period).

The study will be completed in approximately 48 weeks.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. The study completion date is used to ascertain timing for study results posting and reporting.

A completer is a subject who completes up to and including Visit 5 with at least 72 days of randomized treatment.

3.3 Sites and Regions

Approximately 30 sites in the US will participate.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

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

- Inferior corneal fluorescein staining score ≥0.5 (0-4 point scale with allowance for 0.5 point increments)
- Schirmer Tear Test (without anesthesia) ≥1 and ≤10mm

4.1.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met.

1. Known hypersensitivity to investigational product or its components.
2. Prior participation in a lifitegrast (SHP606, SPD606, SAR 1118) clinical study.
3. Subjects who are employees at the investigational site.
4. Subjects who are members of the same household.
5. Subjects with DED secondary to scarring (such as that seen with irradiation, alkali burns, Stevens-Johnson syndrome, cicatrical pemphigoid) or destruction of conjunctival goblet cells (as with vitamin A deficiency). Subjects with incidental scars secondary to refractory surgery (i.e. laser-assisted in situ keratomileusis [LASIK] surgery) that, in the opinion of the investigator, will not interfere with study compliance and/or outcome measures are NOT excluded from the study.
6. Any ocular condition that, in the opinion of the investigator, could affect study parameters including, but not limited to, lid margin disorders (e.g., blepharitis including staphylococcal, demodex, or seborrheic; meibomian gland disease, excessive lid laxity, floppy eyelid syndrome, ectropion, entropion), advanced conjunctivochalasis, Salzmann's nodular degeneration, and asthenopia-related conditions, glaucoma, diabetic retinopathy, follicular conjunctivitis, iritis, uveitis, wet- exudative age-related macular degeneration, retinal vein occlusion, tinea versicolor, and/or active ocular inflammation.
7. Currently active or history of ocular herpes or any other ocular infection within 30 days of the Screening Visit (Visit 1).
8. Any known history of immunodeficiency disorder, human immunodeficiency virus, hepatitis B or C, evidence of acute active hepatitis A (antihepatitis A virus immunoglobulin M), or organ or bone marrow transplant.
9. Any other significant illness that, in the opinion of the investigator, could interfere with the study parameters, including, but not limited to, severe cardiopulmonary disease, poorly controlled hypertension, and/or poorly controlled diabetes.
10. Subjects with secondary Sjögren's syndrome (e.g., rheumatoid arthritis, systemic lupus erythematosis) are eligible provided the subject meets all other inclusion and exclusion criteria, AND, are not in a medical state that, in the opinion of the investigator, could interfere with study parameters, are not taking systemic/ocular steroids, and are not immunodeficient/immunosuppressed (e.g., receiving immunosuppressive drugs to manage their baseline medical state).

11. Any known history of alcohol and/or drug abuse within 12 months prior to the Screening Visit (Visit 1) that, in the opinion of the investigator, may interfere with study compliance, outcome measures, safety parameters, and/or the general medical condition of the subject.
12. Positive urine pregnancy test or nursing an infant (female subjects only).
13. Any blood donation or significant loss of blood within 56 days of the Screening Visit (Visit 1) or during the study.
14. Use of any topical medication and/or antibiotic for the treatment of blepharitis or meibomian gland disease during the study.
15. Use of any investigational product or device within 30 days prior to the Screening Visit (Visit 1) or during the study.
16. Use of the following medications (topical, topical ophthalmic, systemic, and/or injectable) within the time associated washout restrictions below or during the study:
    - Topical cyclosporine: within 6 weeks prior to the Screening Visit (Visit 1).
    - Any medication (oral or topical) known to cause ocular drying: within 30 days of Visit 1 unless the subject has been receiving a stable dose over the past 30 days with no change in dose anticipated during the study period.
    - Oral aspirin or aspirin-containing products: within 30 days of the Screening Visit (Visit 1) unless the subject has been receiving a stable dose over the past 30 days prior to Visit 1 with no change in dose anticipated during the study period.
    - Corticosteroids or mast cell stabilizers (including ocular): within 14 days prior to the Screening Visit (Visit 1).
    - Any medication (oral or topical) known to cause ocular drying that has not been administered as a stable dose for at least 30 days prior to the Screening Visit (Visit 1) and during the study; antihistamines are not allowed at any time during the study
    - Antihistamines (including ocular): within 72 hours prior to the Screening Visit (Visit 1) and throughout the subject's participation during the study.
    - All other topical ophthalmic preparations (including artificial tear substitutes): within 72 hours prior to the Screening Visit (Visit 1).
17. Unwilling to avoid wearing contact lenses during the study.
18. History of LASIK or similar type of corneal refractive surgery within 12 months prior to Visit 1, and/or any other ocular surgical procedure within 12 months prior to Visit 1; or any planned ocular surgical procedure during the study period.
19. History of yttrium aluminum garnet-laser posterior capsulotomy in past 6 months prior to Visit 1.
20. Non-compliance (<80% or >120%) with placebo regimen during the Run-in Period.
21. Missing or unaccounted for ampules during the Run-in Period.

4.2 Reproductive Potential

4.2.1 Female Contraception

Females must have a negative urine pregnancy test at the Screening Visit (Visit 1) and prior to randomization.

Female subjects should be either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years age).
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- All other females must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception throughout the study period and for 30 days following the last dose of investigational product.
- Acceptable methods of contraception are:
  - Abstinence. Females who are not sexually active at the Screening Visit (Visit 1) must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.
  - Intrauterine devices plus condoms.
  - Double-barrier methods (e.g., condoms and diaphragms with spermicidal gel or foam).
  - Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the Screening Visit (Visit 1), plus condoms. If hormonal contraceptives are used they should be administered according to the package insert.
  - Note: If a subject begins using a hormonal contraceptive during the study, they should use one of the other acceptable methods noted above, in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.3 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor if necessary.

If investigational product is discontinued, regardless of the reason, the evaluations listed for the ET Visit are to be performed as completely as possible. Comments (spontaneous or

elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and the total amount of investigational product taken must be recorded in the CRF and source documents.

Subjects who discontinue will not be replaced.

4.3.1 Subject Withdrawal Criteria

Subjects who do not return investigational product or are non-compliant (<80% or >120% between visits) after 2 consecutive visits must be discontinued.

4.3.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- Death
- Lost to follow-up
- Non-compliance
- Pregnancy
- Erroneously admitted into the study or did not meet entry criteria
- Adverse event
- Other (If "Other" is selected, the investigator must specify on the CRF).

4.3.3 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

Prior and concomitant treatment must be recorded on the appropriate CRF page as indicated below. The investigator will categorize treatments as ocular (specified as left eye, right eye or both eyes) or non-ocular based on the indication for use.

5.1 Prior Treatment

Prior treatment includes all treatments used for any reason prior to the study as indicated below:

A lifetime history of all medications/treatments used for DED should be recorded. Subjects must have a history of recent artificial tear use, defined as within 30 days, but not during the 72 hours, prior to Screening Visit (Visit 1) to be eligible for the study.

All medications/treatments used for other ocular indications as well as medications/treatments used for non-ocular indications received within 60 days prior to the Screening Visit (Visit 1) should be recorded.

The investigator will categorize treatments as ocular (specified as left eye, right eye, or both eyes) or non-ocular based on the indication for use. Prior treatment information must be recorded on the appropriate CRF page.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the date of consent and the end of the study, inclusive. The investigator will categorize treatments as ocular (specified as left eye, right eye or both eyes) or non-ocular based on the indication for use. Concomitant treatment information must be recorded on the appropriate CRF page.

The investigator may prescribe additional medications during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.1 Permitted Treatment

Medications not indicated as prohibited are permitted, including treatments for general non-excluded medical conditions.

In the event of an emergency, any needed medications may be prescribed without prior approval, but the medical monitor must be notified of the use of any prohibited medications immediately thereafter.

5.2.2 Prohibited Treatment

Table 2 details the time associated restrictions for common prior treatments that are excluded medications for this study.

Table 2: Common Excluded Treatments and Associated Washout Periods

	Minimum Time Prior to First Open-label Placebo Dose				
Treatment	**6 weeks**	**30 days**	**14 days**	**3 days**	
Topical cyclosporine	X				
Oral aspirin or aspirin-containing products*		X			*unless the subject has been receiving a stable dose over the past 30 days prior to the Screening Visit (Visit 1) with no change in dose anticipated during the study period
Any medication (oral or topical) known to cause ocular drying*		X			*unless administered as a stable dose for at least 30 days prior to the Screening Visit (Visit 1) and during the study
Corticosteroids or mast cell stabilizers (including ocular)			X		
Antihistamines (including ocular)*				X	*and throughout the subject's participation during the study
All other topical ophthalmic preparations (including artificial tear substitutes)*				X	*and throughout the subject's participation during the study

Treatments not listed in Table 2 are considered permitted.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The investigational product is SHP606 (lifitegrast ophthalmic solution, 5.0%), which will be provided as an eye drop. Additional information is provided in the current SHP606 Investigator's Brochure.

The reference/comparator product is placebo, which will also be provided as an eye drop.

6.1.1 Masking the Treatment Assignment

Investigational product will be supplied as a sterile, clear, colorless to pale yellow liquid solution in single dose, 0.99mL low-density polyethylene unit dose ampules with a fill volume of approximately 0.25mL. Each mL of 5.0% solution contains 50mg of lifitegrast active pharmaceutical ingredient. In addition to lifitegrast, the components of the investigational product solution are: sodium chloride, sodium thiosulfate, sodium phosphate, and sterile water. The ingredients have been pH adjusted.

The placebo solution consists of all components of the investigational product solution with the exception of lifitegrast.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

Interactive response technology will be used for screening and enrolling subjects, recording subject visits, randomization (including stratification factors), investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, return of investigational product, and emergency unmasking.

The investigator or designee will access the IRT system at the Screening Visit (Visit 1) to record subject-specific information (i.e., unique subject number, date of birth, etc.). Subjects will be entered as screen failures or as entering Placebo Run-in Period. For subjects who enter Placebo Run-in Period, IRT will provide the assignment of Placebo Run-in Period medication to dispense.

At the Baseline Visit (Visit 2), the investigator or designee will again access the IRT to either document a screen failure or, if the subject has met all entry criteria, to randomize the subject. Sites will enter stratification criteria information prior to randomization. For randomized subjects, the IRT will provide a medication identification (Med ID) number, i.e., kit number to dispense for treatment. At Visits 3-4, the investigator or designee will access the IRT to obtain kit number(s) to dispense for treatment.

Additionally, at Visit 5 and the ET Visit, the investigator or designee will access the IRT to update the subject's status.

The IRT will also be used for creating, tracking, and confirmation of investigational product shipments. A user manual with specific functions and instructions for the IRT will be provided to the site and site personnel will receive training.

6.2.2 Allocation of Subjects to Treatment

This is a double-masked, placebo-controlled study. 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 investigational product allocated to the subject, once eligibility has been determined.

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 strata using permuted blocks.

Randomization will be centralized across study centers, stratified by Baseline Visit (Visit 2) inferior corneal fluorescein staining score (≤/>1.5) in the study eye and by EDS (</≥ 60) in order to ensure balance amongst the treatment groups. An IRT will be used to facilitate subject randomization accounting for the stratification factors. Upon a subject's qualification to enter the study, his/her Baseline Visit (Visit 2) inferior corneal staining score and EDS will be input into the IRT system to classify the subject into one of the following strata:

- Baseline Visit (Visit 2) inferior corneal fluorescein staining score ≤1.5 in the study eye and EDS <60
- Baseline Visit (Visit 2) inferior corneal fluorescein staining score ≤1.5 in the study eye and EDS ≥60
- Baseline Visit (Visit 2) inferior corneal fluorescein staining score >1.5 in the study eye and EDS <60
- Baseline Visit (Visit 2) inferior corneal fluorescein staining score >1.5 in the study eye and EDS ≥60

The IRT will be used at the Baseline Visit (Visit 2) to assign a randomization number and an investigational product kit number to each subject. The randomization number will be used by the IRT at Visit 3 and Visit 4 to obtain an appropriate investigational product kit number for drug resupply. At each visit, the IRT will be used to maintain the subject's status (i.e., screen failure, randomized, completed, or early withdrawal).

6.2.3 Dosing

Placebo or randomized treatment will be administered to the ocular surface twice daily as a single drop in each eye administered upon awakening and just before bedtime. During the Screening Period (Visit 1), subjects will receive open-label placebo. During the Treatment Period, subjects will receive double-masked 5.0% lifitegrast ophthalmic solution or placebo.

Investigational product will be administered at the study site on days of office visits (subjects will be asked not to self-administer one of their doses on visit days). Only 1 dose will be administered on the day of Visits 1 and 5. At the Screening Visit (Visit 1), for training purposes, subjects will self-administer open-label placebo under the supervision of trained study personnel.

At Visits 2-5, investigational product will be administered by trained study personnel. On the day of Visit 2, the first dose will be considered part of the Placebo Run-in Period and the subsequent dose will be considered part of the Randomized Treatment Period. Both doses will be administered at the study site.

All other doses of investigational product will be self-administered.

Site personnel will record the date and time of the first dose in the source documents and will record this information in the appropriate CRF.

6.2.4 Unmasking the Treatment Assignment

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 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 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 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.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification are applied to the investigational product(s) container.

All investigational product is labeled with a minimum of the ***protocol number, medication identification number dosage form (including product name and quantity in pack), directions for use, storage conditions, expiry date (if applicable), batch number and/or packaging reference***, the statements 'For clinical trial use only', and/or 'CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use', 'Keep Out of Reach of Children' and the sponsor name/address.

Space is allocated on the subject kit label so that the site representative can record the subject initials and date dispensed

Additional labels (e.g., those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

6.3.2 Packaging

Investigational product is packaged in labeled containers. Aluminum foil pouches will be labeled and contain 5 unit dose ampules per pouch. Seven labeled pouches will be placed into a labeled carton which will comprise 1 subject kit for a 2-week interval.

Unit dose ampules are for SINGLE USE ONLY and are not labeled.

Changes to sponsor-supplied packaging may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

At the study site, all IP must be stored under the labeled storage conditions in a secure area accessible only to the designated qualified clinical site personnel.
All IP must be stored and inventoried and the inventories must be carefully and accurately documented according to applicable state, federal, and local regulations, ICH Guidelines, GCPs, and study procedures.

Investigational product should be stored at USP Controlled Room Temperature 20-25º C (68-77º F) with excursions permitted to 15º-30º C (59º-86º F)). Store ampules in the foil pouch until administration.

6.4 Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist or study coordinator) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will both administer and dispense the investigational

product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All administered and dispensed medication will be documented on the CRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects. The investigator or his/her designee will enter the unique subject identifier and initials on the investigational product kit labels as they are assigned and dispensed.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the mask of the study is not compromised.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated CRO). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (i.e., IRT) do not require a shipment form. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., ampules in foil pouch) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details (including missing ampules) on the drug accountability form.

Visit to visit compliance will be assessed by site personnel. Site personnel must review the returned investigational product to assess compliance at every visit prior to dispensing

additional investigational product. Any discrepancies should be reconciled with the subject immediately. Subjects who do not return their used and unused should be reminded to bring all used and unused investigational product at their next visit.

Subjects who do not return investigational product or are non-compliant (<80% or >120% between visits) after 2 consecutive visits, must be withdrawn from the study.

Overall compliance will be calculated by the sponsor programmatically at the end of the study.

7. STUDY PROCEDURES

7.1 Study Schedule

The detailed study procedures/assessments to be performed throughout the study are outlined in the Schedule of Assessments (see Table 1) and must be referred to in conjunction with the instructions provided in this section.

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the subject (as per local requirements). There must be documentation of consent (as per local requirements) indicating that the subject is aware of the investigational nature of the study and the required procedures and restrictions, prior to performing any study-related procedures.

7.1.1 Screening Period (Days -14 to -1)

The Screening Period will allow for the determination of eligibility of each subject's inclusion into the study. The Screening Period consists of the Screening Visit (Visit 1) as well as the 14-day, Open-label, Placebo Run-in Period to assess the subject's ability to comply with twice daily medication administration.

A washout period may be required to discontinue any prohibited medication or treatments (see Section 5.2.2 and Table 2 for more details). A subject should not be instructed to wash out any medication or treatment for this study until after informed consent has been obtained. Subjects should not stop permitted medications or treatments that are effective and well tolerated to participate in this study.

The Screening Period will be approximately 14 days (with a minimum of 11 days and a maximum of 17) days, during which all procedures listed for the Screening Visit (Visit 1) in Table 1 shall be completed. 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 all screening assessments required to confirm initial eligibility are complete. Extensions to the screening window to

accommodate washout timeframes will be discussed on a case by case basis with the medical monitor and some screening assessments may need to be repeated.

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been randomized or administered randomized investigational product. Screen failures can occur at the Screening or Baseline Visits. Subjects cannot be rescreened once they have been designated as a screen failure.

7.1.1.1 Screening Visit (Visit 1): Day -14

The Screening Visit (Visit 1) assessments will be performed as outlined in Table 1.

The investigator or assigned site staff will access the IRT to register the subject's unique 6-digit subject identification number, record subject-specific information (i.e., date of birth, etc.). A urine pregnancy test will be completed for all females. The results will be read by site personnel and recorded in the source documents.

All AEs occurring after signature of informed consent must be recorded in the source documents and CRF.

If the subject does not meet eligibility criteria following completion of screening assessments, the investigator or designee will document the subject as a screen failure, including the IRT.

Subjects who meet eligibility criteria at the end of the Screening Visit (Visit 1) will enter the 2-week Open-label, Placebo Run-in Period. Site personnel will access the IRT to obtain information about assignment of the Placebo Run-in Period. Approximately 15 minutes after the last assessment, for training purposes, subjects will self-administer open-label placebo under the supervision of trained study personnel. Only 1 dose will be administered on the day of Visit 1 and subjects will be instructed not to administer a second dose at home that evening.

7.1.2 Baseline Visit (Visit 2): Day 0

The Baseline Visit (Visit 2) assessments will be performed as outlined in Table 1.

Subjects will return to the site for the Baseline Visit (Visit 2) to confirm eligibility.

Inclusion/exclusion criteria will be re-evaluated at the Baseline Visit (Visit 2) to ensure subjects continue to meet eligibility criteria. Subjects who continue to meet all eligibility criteria will be randomized. Subjects who fail to meet eligibility criteria at the Baseline Visit (Visit 2) will be considered screen failures.

A urine pregnancy test will be completed for all females. The results will be read by site personnel and recorded in the source documents.

The investigator or designee will perform drug accountability (assessed at the packaging level) using the returned used and unused investigational product. The pharmacist/nominated person will record details (including missing ampules) on the drug accountability form. Any discrepancies should be reconciled with the subject immediately. Subjects must return all ampules and be between 80-120% compliant to be eligible for the study. Prior to randomization, the following procedures should be performed: conjunctival redness score assessment, VAS assessment, ocular discomfort score assessment, [redacted], BCVA, slit lamp biomicroscopy, corneal fluorescein staining, conjunctival staining (lissamine green) and STT. The VAS should be completed first. Approximately 15 minutes following the completion of the last screening assessment, placebo drops will be administered by trained site personnel.

For subjects who continue to meet eligibility criteria, the investigator or assigned site staff will access the IRT to randomize the subject. The IRT system will assign the randomization number and the MED ID number to dispense to the subject, accounting for the stratification factors of the subject's baseline inferior corneal fluorescein staining and EDS.

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

Site personnel will record the date and time of the first dose in the source documents and will record this information in the appropriate CRF.

The drop comfort assessment will be performed following the administration of randomized investigational product.

Any AE that occurs during this visit will be recorded in the CRF and considered a TEAE.

7.1.3 Treatment Period (Visits 3-5): Weeks 2, 6, and 12/Days 1-84

The Visit 3-5 assessments will be performed as outlined in Table 1.

A ±3-day visit window is permitted during this period. Visit windows are calculated based upon the date of randomization (the Baseline Visit [Visit 2]).

At each visit, the investigator or designee will access the IRT system to assign the investigational product that should be dispensed.

7.1.3.1 Visits 3 and 4 (Weeks 2 and 6)/Days 14 and 42

The Visit 3-4 assessments will be performed as outlined in Table 1.

Site personnel must confirm that subjects have not administered the morning dose of investigational product prior to the office visit.

The investigator or designee will perform drug accountability (assessed at the packaging level and since the last visit) using the returned used and unused investigational product prior to dispensing additional investigational product.

The pharmacist/nominated person will record details (including missing ampules) on the drug accountability form.

Any discrepancies should be reconciled with the subject immediately. Subjects who do not return their used and unused should be reminded to bring all used and unused investigational product at their next visit.

Subjects who do not return investigational product or are non-compliant (<80% or >120% between visits) after 2 consecutive visits, must be withdrawn from the study.

At Visits 3 and 4, trained site personnel will administer the dose of randomized investigational product within 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 administer the second dose of randomized investigational product at home that evening.

7.1.3.2 Visit 5 (Week 12)/Day 84

The Visit 3-5 assessments will be performed as outlined in Table 1.

A urine pregnancy test will be completed for all females. The results will be read by site personnel and recorded in the source documents.

The VAS should be the first ophthalmologic assessment completed. The BCVA and slit lamp evaluation will be completed before and after administration of investigational product. The dilated fundoscopy should be the final ophthalmologic assessment completed.

Site personnel must confirm that subjects have not administered the morning dose prior to the office visit.

At Visit 5, trained site personnel will administer the dose of randomized investigational product within 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. Only 1 dose of investigational product will be administered on the day of Visit 5.

The [redacted] should be the final assessment performed.

All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1). If a non-serious, ocular AE remains unresolved at the conclusion of the subject's participation in the study, the investigator or designee should contact the medical

monitor and make a joint clinical assessment as to whether continued follow-up of the AE is warranted, and the results of this assessment must be documented.

7.1.4 Early Termination Visit

The ET assessments will be performed as outlined in Table 1.

All subjects will be asked to return for the safety and efficacy assessments scheduled for the ET Visit.

The VAS should be the first ophthalmologic assessment completed. The dilated fundoscopy should be the final ophthalmologic assessment completed.

The investigator or designee will perform drug accountability using the returned investigational product and reconcile any discrepancies with the subject immediately. Investigational product will not be administered at the ET Visit.

The [redacted] should be the final assessment performed.

All AEs and SAEs that are not resolved at the time of this contact will be followed to closure (see Section 8.1). If a non-serious, ocular AE remains unresolved at the conclusion of the subject's participation in the study, the investigator or designee should contact the medical monitor and make a joint clinical assessment as to whether continued follow-up of the AE is warranted, and the results of this assessment must be documented.

7.1.5 Additional Care of Subjects After the Study

No aftercare is planned for this study.

7.2 Study Evaluations and Procedures

The full title, version, and approximate time required for completion of the scales used in this study are detailed in Appendix 1.

All assessments listed below will be performed by the subject and/or a qualified/trained site staff as indicated in the assessment description. For subject-completed assessments, trained site staff should not assist the subject in completing assessments in such a manner that it would influence their responses. Site staff should review the completed assessment to ensure completeness.

If an answer is marked in error, the subject may correct it by drawing a single line through the error and initialing and dating the change; however, corrections can only be made to scales by the subject during a study visit and changes must not be made to subject-completed scales

after the visit has been completed. Assessments are to be performed according to the schedule shown in Table 1.

It is critical that assessments are completed by the same qualified/trained site staff member throughout the study. Every effort must be made to ensure consistency. In the event that a change in qualified clinician rater is required for a visit, the change will be noted in the source documents.

7.2.1 Demographic and Other Baseline Characteristics

7.2.1.1 Height and Weight

Self-reported height and weight and medical history will be collected and recorded on the CRF.

7.2.1.2 Medication and Medical History

Medication History
Refer to Section 5 for full details on collection of prior treatment.

The investigator will categorize treatments as ocular (specified as left eye, right eye or both eyes) or non-ocular based on the indication for use. Prior treatment information must be recorded on the appropriate CRF page.

Medical History
The investigator must record all clinically or medically relevant information regardless of how much time has elapsed since the date of any diagnosis. Medical history will be classified as ocular or non-ocular by the investigator. The ocular medical history must include a current diagnosis of DED. History should include, but is not limited to:

- Lifetime history of ocular diseases/conditions.
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, and any other non-ocular diseases/underlying conditions within the past year prior to the Screening Visit (Visit 1).

7.2.2 Efficacy

7.2.2.1 Visual Analogue Scale

The VAS will be performed during the study as outlined in Table 1.

Subjects will be asked the following questions regarding their current ocular discomfort (unrelated to investigational product instillation) at all visits for the 7 items of burning/stinging, itching, foreign body sensation, eye discomfort, eye dryness, photophobia, and pain.

The subject will be asked to subjectively rate each ocular symptom (oculus uterque) by placing a vertical mark on the horizontal line to indicate the level of discomfort. Zero percent corresponds to "no discomfort" and 100 corresponds to "maximal discomfort."

Burning/Stinging	0	50	100
Itching	0	50	100
Foreign body sensation	0	50	100
Eye Discomfort	0	50	100
Eye Dryness	0	50	100
Photophobia	0	50	100
Pain	0	50	100

7.2.2.2 Ocular Discomfort Score Assessment

The ocular discomfort score assessment will be performed during the study as outlined in Table 1.

Assessment of ocular discomfort scores will be conducted by site personnel and will be subjectively graded by the subjects according to the following 5-point scale (rating each eye separately):

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

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

7.2.3 Safety

7.2.3.1 Conjunctival Redness Score Assessment

The conjunctival redness score assessment will be performed during the study as outlined in Table 1.

Conjunctival redness will be graded for each eye according to the following scale with allowances for 0.5 point increments:

None	0 = none, no vasodilation
Trace	1 = slight vasodilation of the ciliary or conjunctival vessels
Mild	2 = diffuse vasodilation of ciliary vessels
Moderate	3 = diffuse ciliary and trace horizontal vasodilation of conjunctival vessels
Severe	4 = diffuse ciliary vasodilation with conspicuous vasodilation of horizontal conjunctival vessels

7.2.3.2 Corneal Fluorescein Staining

The corneal fluorescein staining will be performed during the study as outlined in Table 1.

The purpose of this procedure is to grade the degree of corneal epithelial cell injury as measured by fluorescence using slit lamp examination. This procedure will be performed and assessed by trained site personnel.

Procedure

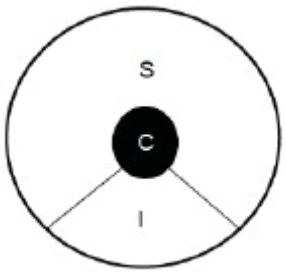
- A 5.0µL volume of 2% unpreserved sodium fluorescein is instilled into the lower conjunctival sac using a micropipette (sterile tip) or glass capillary tube.
- After approximately 5 minutes following instillation of fluorescein, the corneal

fluorescein grade is obtained of each eye using a 0-4 point scale (with 0.5 point increments).

- The upper eyelid is slightly lifted to assess the whole corneal surface.
- A blue light and a #12 Wratten yellow filter must be used to view the eye.
- It is recommended that the same investigator evaluate the same subject using the same slit lamp/settings at all study visits.

Corneal Fluorescein Staining Score

The corneal surface is divided into 3 regions as diagrammed.



Outside circle includes limbal margin

S = superior region

C = central region

I = inferior region

Score each of the 3 regions of both eyes using the modified grading scale of 0-4 with 0.5 grade increments and the description provided to achieve a closest approximation (best fit).

None	0 = no staining
Trace	1 = few/rare punctate lesions
Mild	2 = discrete and countable lesions
Moderate	3 = lesions too numerous to count but not coalescent
Severe	4 = coalescent

Reference: modified from Lemp (1995) and Shimmura (1995)

7.2.3.3 Conjunctival Staining with Lissamine Green

The conjunctival staining with lissamine green will be performed during the study as outlined in Table 1.

The purpose of this procedure is to grade the degree of conjunctival epithelial cell injury as measured by lissamine green using slit lamp examination. This procedure will be performed and assessed by trained site personnel.

Procedure

- A 10µL volume of lissamine green solution is instilled into the inferior conjunctival cul-de-sac.
- The subject will be instructed to blink several times to distribute the lissamine green.
- After approximately 30 seconds following instillation of lissamine, the staining will be graded using a 0-4 point scale (with 0.5 point increments).

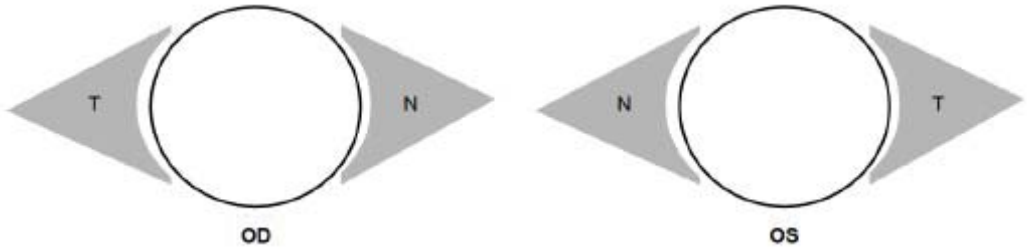
Conjunctival Staining Score Assessment

The conjunctival surface is divided into 2 triangular segments (gray region) as diagrammed below.

T (temporal region) = wedge of temporal conjunctiva

N (nasal region) = wedge of nasal conjunctiva

Circle represents limbal margin of the cornea:



Score each of the **2** regions of both eyes using the modified grading scale of 0-4 with 0.5 grade increments and the description provided to achieve a closest approximation (best fit).

None	0 = no staining
Trace	1 = few/rare punctate lesions
Mild	2 = discrete and countable lesions
Moderate	3 = lesions too numerous to count but not coalescent
Severe	4 = coalescent

Reference: modified from Lemp (1995) and van Bijsterveld, (1969)

7.2.3.4 Schirmer Tear Test

The STT will be performed during the study as outlined in Table 1.

Schirmer Tear Test will be performed according to the following procedure:

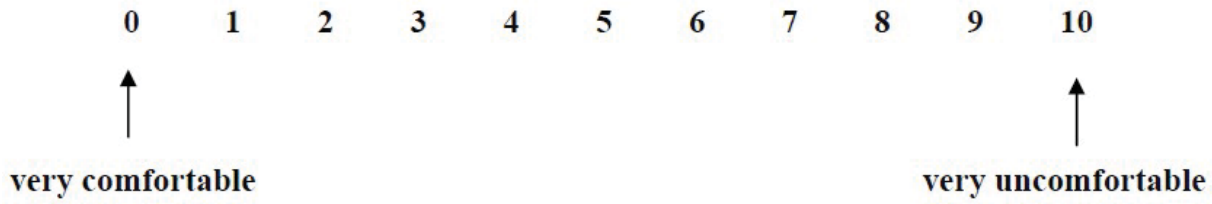
- Using a sterile Tear Flo Schirmer test strip (Rose Enterprises), a bend in the strip will be made in line with the notch in the strip.
- The subject will be instructed to gaze up and in
- The Schirmer test strip will be placed in the lower temporal lid margin of each eye such that the strip fits tightly. Subjects will be instructed to close their eyes.
- After 5 minutes have elapsed, the Schirmer strip will be removed. The length of the moistened area will be recorded (mm) for each eye.

7.2.3.5 Drop Comfort Assessment

The drop comfort assessment will be performed during the study as outlined in Table 1.

The purpose of evaluating the drop comfort by the subject is to assess the degree of initial comfort of the instilled eye drop (placebo versus lifitegrast).

Evaluation of the comfort of the eye drop will be conducted for each eye immediately and at 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 or the subject has an interruption or discontinuation of investigational product, it should be recorded as an AE.



Reference: Torkildsen (2008)

7.2.3.6 Best Corrected Visual Acuity

The BCVA will be performed during the study as outlined in Table 1.

- Visual acuity will be assessed prior to slit lamp examination.
- Visual acuity will be assessed using an ETDRS format wall chart under normal room illumination using the logMAR scoring system. The procedure used will be consistent with the recommendations provided for using the ETDRS eye chart. To ensure consistency in responses during the study, VA assessments must be done using the same testing conditions (e.g., same lighting conditions) and same spectacle correction throughout the study; if there is a change in the testing conditions (e.g., subject forgets eyeglasses), the reason for the change should be documented.

- Visual acuity testing will be tested with the subject wearing his/her current spectacle correction, therefore, the subject should be queried as to whether he/she requires correction for distance vision (e.g., driving); if so, the subject will be tested with glasses. The subject should be reminded to bring the same pair of glasses to each study visit. If the subject forgets to bring glasses, VA will be tested using the pinhole occluder and the results recorded as "with pinhole".
- If the examiner needs to repeat the VA assessment (at same visit) for technical reasons (e.g., subject has difficulty reading chart and it is recognized that the eyeglasses are soiled/smudged after the test was conducted, or subject failed to understand instructions properly), the examiner, at his/her professional discretion, is allowed to choose the single set of VA scores that best represents the subject's VA for that visit. This should be clearly documented in the subject's source documents.

Equipment

For purposes of standardizing the testing conditions during the study, all sites must use ETDRS 2000 Series Charts 1 and 2. For reflectance (wall) charts, the chart should be placed frontally and well illuminated.

Visual Acuity Measurement Technique

The distance from the subject's eyes to the VA chart is 4 meters and the subject may sit or stand. The examiner should ensure the subject is comfortable and the head is not moving forward/backward during testing and that the eyes remain at the same distance from the chart throughout the test. If the subject requires multifocal corrective glasses, the examiner should confirm that the subject is viewing the chart with the distance segment.

Pre-testing instruction should include informing the subject that the chart has letters only. To achieve the best identification of each letter, the examiner should remind the subject to read the chart slowly; the subject should not proceed to the next letter until giving a definitive response.

The left eye is occluded and testing begins with the right eye (Chart 1). The subject should attempt to read each letter, line-by-line, left-to-right, beginning with line 1 at the top of the chart. If the subject reads a number, the examiner should remind the subject that the chart contains only letters and then request a letter instead.

If the subject changes a response (e.g., 'that was a "C" not an "O"') before he/she has read aloud the next letter, then the change must be accepted. If the subject changes a response having read the next letter, then the change is not accepted. The examiner should never point to the chart or to specific letters on the chart during the test.

When the subject says he/she cannot read a letter, the subject should be encouraged to guess. If the subject identifies a letter as 1 of 2 letters, he/she should be asked to choose one letter. When it becomes evident that no further meaningful readings can be made, despite encouragement to read or guess, the examiner should stop the test for that eye.

After the test for the right eye is completed, occlude the right eye. The test is then repeated for the left eye (Chart 2).

Further instruction for performing the BCVA is in Appendix 2. Changes in VA will be assessed for clinically significance. Clinically significant changes should be recorded in the source and on the eCRF as an AE.

7.2.3.7 Slit Lamp Biomicroscopy

Slit lamp biomicroscopy will be performed during the study as outlined in Table 1.

Observations will be graded as Normal or Abnormal. Abnormal findings will be described, and clinically significant abnormalities should be recorded in the source and on the eCRF as an AE. The following will be examined at each visit:

- Cornea
- Conjunctiva
- Anterior Chamber
- Iris
- Lens
- Lid

External examination and biomicroscopy will be performed using a slit lamp. Magnification will be consistent with standard clinical practice. The subject will be seated.

7.2.3.8 Dilated Fundoscopy

A dilated fundoscopy examination will be performed during the study as outlined in Table 1.

The investigator will instill 1 drop of 1% tropicamide bilaterally and wait approximately 15 minutes or when the subject's eyes are deemed sufficiently dilated in the opinion of the investigator. Observations will be graded as Normal or Abnormal. Abnormal findings will be described. Clinically significant abnormalities will be recorded as an AE.

The following will be examined:

- Vitreous
- Retina
- Macula
- Choroid

- Optic Nerve

7.2.3.9 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g., "Have you had any health problems since your last visit?"). Adverse events are collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.) Adverse events will be classified as ocular or non-ocular by the investigator.

7.2.3.10 Pregnancy Test

A urine pregnancy test will be performed on all females during the study as outlined in Table 1.

A urine pregnancy test is performed on all females at all scheduled visits, if pregnancy is suspected, or on withdrawal of the subject from the study. Urine pregnancy test kits will be provided by the sponsor and read on site by qualified site personnel.

7.2.4 Health-related Quality of Life Assessment

[redacted]

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the final visit stated in Section 7.1.3.2 or ET Visit stated in Section 7.1.4. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE CRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

If a non-serious, ocular AE remains unresolved at the conclusion of the subject's participation in the study, the investigator or designee should contact the medical monitor and make a joint clinical assessment as to whether continued follow-up of the AE is warranted, and the results of this assessment must be documented.

- The investigator will categorize AEs as ocular (specified as left eye, right eye or both eyes) or non-ocular.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and

more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, the AE should be categorized according to the guidelines below. The causality assessment must be documented in the source document.

Guidelines for assessing relationship:

Relationship	**Description**
Not Related	Exposure to the IP has not occurred. OR The administration of the IP and the occurrence of the AE are not reasonably related in time. OR The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts [evidence] or arguments to suggest a causal relationship to the IP.

Possibly Related	The administration of the IP and the occurrence of the AE are reasonably related in time. AND The AE could not be explained equally well by factors or causes other than exposure to the IP.
Probably Related	The administration of IP and the occurrence of the AE are reasonably related in time. AND The AE is more likely explained by exposure to the IP than by other factors or causes.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown.

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. This could include progression of disease which impacts the ability to perform activities of daily living.

8.1.5 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the subject's last visit (Visit 5 or ET).

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Pharmacovigilance Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products

Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Shire medical monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Trial Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Trial Serious Adverse Event Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or ultrasound result will determine the pregnancy onset date.

8.1.6 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of >4 ampules/day of the product.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

- The administration and/or use of the unassigned treatment is always reportable as a medication error.
- The administration and/or use of an expired investigational product should be considered a reportable medication error.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator's brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Pharmacovigilance Department and the Shire medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.6) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Trial Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Shire Pharmacovigilance Department. A copy of the Shire Clinical Trial Serious Adverse Event Form (and any applicable follow-up reports) must also be sent to the Shire medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

An **SAE** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not

refer to an event which hypothetically might have caused death if it was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the subject's last visit (Visit 5 or ET), and must be reported to the Shire Pharmacovigilance Department and the Shire medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Pharmacovigilance Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and/or CRO is responsible for notifying the relevant regulatory authorities/US central IRB of related, unexpected SAEs.

In addition, the sponsor and the clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP606 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the investigator's meeting, site initiation visit, and throughout the study. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRF Completion Guidelines. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unmask the treatment assignment (i.e., investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unmasking, any data that may unmask study team personnel will be presented as masked information or otherwise will not be made available. If applicable, unmasked data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The statistical analysis plan will also include a description of how missing, unused, and spurious data will be addressed.

The statistical analysis plan will be finalized prior to unmasking to preserve the integrity of the statistical analysis and study conclusions.

All statistical analyses will be performed after the database is locked and unmasked.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513) Version 9.1 or higher.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or data monitoring committee in this study.

9.6 Sample Size Calculation and Power Considerations

The sample size was estimated for the primary and key secondary comparisons of lifitegrast ophthalmic solution (5.0%) to placebo by using nQuery Advisor 7.0.

A sample size of 350 subjects per treatment group (total 700 subjects) will ensure more than 90% power 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 5.0% type I error.

The sample size of 350 subjects per treatment group will also ensure more than 85% power to detect a difference of 8.0 units (with standard deviation of 34) in mean change from baseline to Day 42 between the treatment groups and more than 80% power to detect a difference of 6.5 units (with standard deviation of 30) in mean change from baseline to Day 14 between the treatment groups.

It is expected that no subject will be excluded from the primary efficacy analysis due to missing data given that the primary analysis is based on LOCF of on-treatment assessment.

9.7 Study Population

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

The **Randomized Population** will consist of all subjects in the Screened Set for whom a randomization number has been assigned.

The **ITT Population** will consist of all subjects who have taken at least 1 dose of investigational product and have at least 1 post-baseline (e.g., randomization) primary efficacy assessment.

The **Safety Population** will consist of all subjects who have taken at least 1 dose of investigational product.

9.8 Efficacy Analyses

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

Efficacy data collected at the Baseline Visit (Visit 2) will be used as the baseline for all efficacy analyses.

9.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be analyzed based on the ITT Population with LOCF.

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

The null hypothesis to be tested is that there is no difference for the primary efficacy endpoint between lifitegrast and placebo with the alternative of a non-zero difference between them.

The primary analysis of change from baseline to Day 84 in EDS will be performed using a 2-sample t-test from ANOVA model comparing lifitegrast ophthalmic solution to placebo in the ITT Population with LOCF. The stratification factors used for randomization will be used for this analysis. The ANOVA model will include treatment, strata and the interaction between treatment and strata.

The stratified, 2-sample t-test will be performed using the LSMEANS statement in PROC MIXED with the option to specify weights for combining the between-treatment group estimate from each stratum. The between-treatment group estimates from each stratum will be combined using the number of subjects in each stratum as the weights as proposed by Lin (1999). The individual strata will contribute to the overall analysis proportionate to their size as suggested by Anello (2005). The Type I error rate for rejecting a null hypothesis will be set at a 2-sided alpha level of 5%.

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

9.8.2 Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints will be also analyzed based on the ITT Population with LOCF.

The 2 key secondary efficacy endpoints are defined as the change from baseline to Day 42 in the eye dryness score and change from baseline to Day 14 in the eye dryness score.

The 2 key secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint using the ANOVA model containing treatment and strata.

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

9.8.3 Multiplicity Adjustment

In order to maintain study-wide Type I error control at 2-sided 5% level, the hypothesis testing for the primary and the 2 key secondary efficacy endpoints will be done sequentially [if primary is statistically significant, then the first key secondary (Day 42) will be tested. Subsequently, if the first key secondary is statistically significant, then the second key secondary (Day 14) will be tested].

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 eye dryness score will be tested at 2-sided 5% level. If this first key secondary efficacy endpoint is rejected then the second key secondary efficacy endpoint of change from baseline to Day 14 in eye dryness score will be tested at 2-sided 5% level. A later test can only be reported as significant if all earlier tests are also found significant.

9.8.4 Secondary Efficacy Endpoints

The secondary endpoints will be also analyzed based on the ITT Population with LOCF.

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) in the study eye
- Items of the VAS: burning/stinging, itching, foreign body sensation, eye discomfort, photophobia, pain.

The secondary efficacy endpoints will be analyzed similarly as the primary efficacy endpoint using the ANOVA model containing treatment and strata.

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

9.9 Safety Analyses

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

The safety data collected at the Baseline Visit (Visit 2), or the last preceding visit if not collected at Visit 2, will be used as the baseline value for safety analyses.

Treatment-emergent adverse events are defined as AEs that started or deteriorated on or after the date of the first dose of double-masked, randomized investigational product.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of TEAEs will be calculated overall, by SOC, by

preferred term, and by treatment group. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and listed.

Generally, TEAEs will be presented separated by whether or not the AE was an ocular or non-ocular AE.

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

- Corneal fluorescein staining scores (inferior, superior, central, total)
- Best corrected visual acuity
- Slit lamp biomicroscopy
- Dilated fundoscopy
- Drop comfort scores
- Conjunctival staining (lissamine green)
- Conjunctival redness score
- Schirmer Tear Test
- Pregnancy test

9.10 Other Analyses

9.10.1 Health-related Quality of Life Analyses

[redacted]

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites,

regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and subinvestigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The clinical research associate/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US Food and Drug Administration, EMA, United Kingdom Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US Food and Drug Administration (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the

IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market SHP606; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

APPENDIX 1 SCALES AND ASSESSMENTS

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Completed by
Visual Analogue Scale	Subject
Ocular discomfort score assessment	Subject
Drop comfort assessment	Subject
[redacted]	[redacted]
Best Corrected Visual Acuity Assessment	Site
Slit lamp biomicroscopy	Site
Conjunctival redness score assessment	Site
Corneal fluorescein staining	Site
Conjunctival staining (lissamine green)	Site
Schirmer Tear Test, without anesthesia	Site
Dilated fundoscopy	Site

A separate master file containing source documentation and instructions for each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

APPENDIX 2 BCVA: LOGMAR VISUAL ACUITY CALCULATIONS

The examiner records each letter identified correctly by circling the corresponding letter on the Visual Acuity Worksheet. The examiner records a letter read incorrectly, or a letter for which the subject made no guess, by crossing the letter out with an "X". Each letter read incorrectly is scored as 1 point.

The last line in which a letter is read correctly will be taken as the base logMAR reading. To this value will be added the number "N x 0.02" where 'N' represents the total number of letters missed up to and including the last line read. This total sum represents the logMAR VA for that eye.

For Example: Subject correctly reads 4 of 5 letters on the 0.2 line, and 2 of 5 letters on the 0.1 line.

Base logMar = 0.1

N (total number of letters incorrect on line 0.2 as well as 0.1) = 4

N x T (T=0.02) = 0.08

Base logMAR + (N x T) = 0.1 + 0.08

logMAR VA = 0.18

The following Snellen equivalents will be used to correspond to the logMAR VA:

Visual acuity scales

Foot	Meter	Decimal	LogMAR
20/200	6/60	0.10	1.00
20/160	6/48	0.13	0.90
20/120	6/36	0.17	0.78
20/100	6/30	0.20	0.70
20/80	6/24	0.25	0.60
20/60	6/18	0.33	0.48
20/50	6/15	0.40	0.40
20/40	6/12	0.50	0.30
20/30	6/9	0.63	0.18
20/25	6/7.5	0.80	0.10
20/20	6/6	1.00	0.00
20/16	6/4.8	1.25	-0.10
20/12	6/3.6	1.67	-0.22
20/10	6/3	2.00	-0.30