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Study ID:

KPI-121-C-011

Study Title:

A Phase 3, Double-masked, Randomized, Controlled Study of KPI-121 0.25%  
Ophthalmic Suspension Compared to Vehicle In Subjects With Dry Eye Disease  
(STRIDE 3)

Date:

27 Mar 2019

KPI-121

KPI-121-C-011

A PHASE 3, DOUBLE-MASKED, RANDOMIZED, CONTROLLED STUDY  
OF KPI-121 0.25% OPHTHALMIC SUSPENSION COMPARED TO VEHICLE  
IN SUBJECTS WITH DRY EYE DISEASE (STRIDE 3)

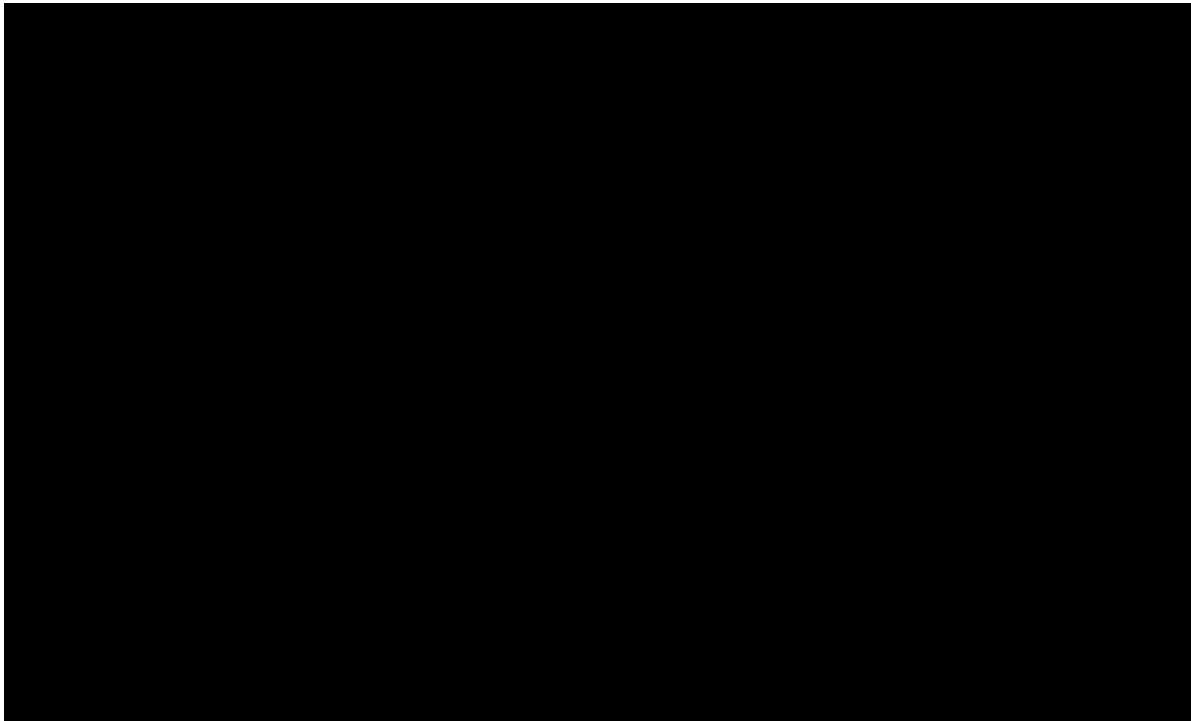
**Sponsor:** Kala Pharmaceuticals, Inc.  
490 Arsenal Way, Suite 120  
Watertown, MA 02472

**Medical Monitor:**



**Issue Date:** Original: 14 Jun 2018  
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Amendment 01: 27 Mar 2019

**Approved:**



## INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for KPI-121. I have read Protocol KPI-121-C-011 (STRIDE 3) dated 27Mar2019 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator

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Signature of Investigator

---

Date

## EMERGENCY CONTACTS

**Table 1: Emergency Contact Information**

<b>Role in Study</b>	<b>Name</b>	<b>Contact information</b>
Clinical Project Manager	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Medical Monitor	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Chief Medical Officer	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
SAE Reporting	[REDACTED]	[REDACTED] [REDACTED]

## 2. SYNOPSIS

<b>Name of Sponsor/Company:</b> Kala Pharmaceuticals, Inc.	
<b>Name of Investigational Product:</b> KPI-121 0.25%	
<b>Name of Active Ingredient:</b> Loteprednol etabonate	
<b>Title of Study:</b> A Phase 3, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease (STRIDE 3)	
<b>Study center(s):</b> Approximately 80 sites will participate in this study.	
<b>Studied period (years):</b> Estimated date first subject enrolled: July 2018 Estimated date last subject completed: Sept 2019	<b>Phase of development:</b> III
<b>Primary Objective:</b> <p>The primary objective of the study is to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects who have a documented clinical diagnosis of dry eye disease.</p>	
<b>Methodology:</b> This is a Phase 3, multi-center, double-masked, randomized, vehicle-controlled, parallel-group study designed to evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension versus vehicle in subjects with dry eye disease.	
<b>Number of subjects (planned):</b> Approximately 3200 subjects will be screened and approximately 900 subjects will be randomized.	
<b>Diagnosis and main criteria for inclusion:</b> <b>Inclusion Criteria:</b> <p>At Visit 1 (Screening) and Visit 2 (Day 1), individuals of either gender or any race will be eligible for study participation if they:</p> <ol style="list-style-type: none"> <li>1. Provide written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to any study-related procedures.</li> <li>2. Are 18 years of age or older.</li> <li>3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study, including: <ol style="list-style-type: none"> <li>a. Single-masked investigational product use compliance of at least 80% during the final week of Stage 1 [REDACTED] AND</li> <li>b. [REDACTED]</li> </ol> </li> <li>4. Have a documented clinical diagnosis of dry eye disease in both eyes.</li> <li>5. Have ongoing dry eye disease as defined by the following criteria in the <b>same eye or both eyes</b>: </li> </ol>	

- a. Total corneal fluorescein staining (CFS) score [National Eye Institute (NEI) scale] at both Visit 1 (Screening) and Visit 2 (Day 1) AND
  - b. assessment of bulbar conjunctival hyperemia [Cornea and Contact Lens Research Unit (CCLRU) scale] at both Visit 1 (Screening) and Visit 2 (Day 1) AND
  - c. Unanesthetized Schirmer Test score of at Visit 1 (Screening) in the same eye as qualified for 5b criterion above AND
  - d. ocular discomfort severity (ODS) at Visit 1 (Screening) AND
  - e. ODS score
  - f.
6. Have normal lid anatomy.
7. Are women of child bearing potential (WOCBP) who are not pregnant or lactating and not sexually active (i.e., abstinent) for 14 days prior to Visit 1 (Screening) and willing to remain so through 30 days following Visit 4 or the last administration of the investigational product or until completion of the subject's first menstrual cycle following the last administration of the investigational product, whichever period of time is longer. Alternatively, WOCBP who are not abstinent must have been using 1 of the following acceptable methods of birth control for the times specified:
- a. Intrauterine device (IUD) in place for at least **3 months** prior to Visit 1 (Screening) and continuing through Visit 4 or last administration of investigational product or until completion of the subject's first menstrual cycle following last administration of the investigational product, whichever period of time is longer.
  - b. Barrier method (condom or diaphragm) with spermicide for at least **3 months** prior to Visit 1 (Screening) and continuing through Visit 4 or last administration of the investigational product or until completion of the subject's first menstrual cycle following last administration of the investigational product, whichever period of time is longer.
  - c. Stable hormonal contraceptive for at least **3 months** prior to Visit 1 (Screening) and continuing through Visit 4 or last administration of the investigational product or until completion of the subject's first menstrual cycle following administration of the investigational product, whichever period of time is longer.
- NOTE:** For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following administration of the investigational product is not applicable as females receiving this form of contraception will not have menses.
- d. In a monogamous relationship with a surgically sterilized (i.e., vasectomized) partner at least **6 months** prior to Visit 1 (Screening) through Visit 4 or last administration of the investigational product or until completion of the subject's first menstrual cycle

following administration of the investigational product, whichever period of time is longer.

8. Are postmenopausal women [i.e., no menstrual cycle for at least one year prior to Visit 1 (Screening)] or are women who have undergone 1 of the following sterilization procedures at least 6 months prior to Visit 1 (Screening):
  - a. Bilateral tubal ligation
  - b. Hysterectomy
  - c. Hysterectomy with unilateral or bilateral oophorectomy
  - d. Bilateral oophorectomy

**Exclusion Criteria:**

In order for subjects to be eligible at Visit 1 (Screening) and Visit 2 (Day 1) they may not:

1. Have a known hypersensitivity or contraindication to the investigational product(s) or their components.
2. Have used any of the following medications or had any of the following procedures within **30 days** prior to Visit 1 (Screening) or for the duration of the study:
  - a. Ocular, inhaled or intranasal corticosteroids
  - b. Ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of  $\leq 81$  mg/day of acetylsalicylic acid (ASA or aspirin)
  - c. Topical ocular antibiotics
  - d. Topical ocular antihistamines or mast cell stabilizers
  - e. Oral antihistamines
  - f. Topical or nasal vasoconstrictors
  - g. Autologous serum tear preparations
  - h. Lipiflow treatment
  - i. TruTear treatment
  - j. Blephex treatment
3. Have used any of the following medications within **60 days** prior to Visit 1 (Screening) or for the duration of the study:
  - Topical cyclosporine (Restasis<sup>®</sup>)
  - Topical lifitegrast
  - Any form of topical loteprednol etabonate (LE)
4. Have altered oral dosing of the following within **30 days** prior to Visit 1 (Screening) or anticipate alteration of dosing during the study:

- a. Tetracycline compounds (e.g., tetracycline, doxycycline, or minocycline)
  - b. Omega-3 or Omega-6 supplements
5. Have altered dosing of the following medications within **6 months** prior to Visit 1 (Screening) or anticipate alteration of dosing during the study:
- a. Anticholinergics
  - b. Anticonvulsants (e.g., topiramate)
  - c. Antidepressants
  - d. Isotretinoin
  - e. Systemic immunosuppressive agents including oral corticosteroids at a dose of prednisone  $\leq 11$  mg/day or equivalent.
- NOTE:** Oral corticosteroid use at a dose of prednisone  $>11$  mg/day or equivalent is excluded.
6. Be unwilling to abstain from the use of any topical ophthalmic medications **at Visit 1 (Screening)** and for the duration of the study, including:
- a. Eyelash growth medications, including both prescription and over-the-counter
  - b. Eye drops, gels, ointments, or artificial tears
7. Be unwilling to abstain from the use of TNF-blocking agents (e.g. etanercept, adalimumab, infliximab) **at Visit 1 (Screening)** and for the duration of the study.
8. Be currently receiving treatment for glaucoma **at Visit 1 (Screening)** or for the duration of the study and/or have history of or current glaucoma, or an IOP over 21mmHg **at Visit 1 (Screening) or Visit 2 (Day 1)**.
9. Be unwilling to abstain from wearing contact lenses for **14 days** prior to Visit 1 (Screening) and for the duration of the study.
10. Be monocular or have a BCVA of +1.0 logMAR or worse as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS).
11. Have had penetrating intraocular surgery within **3 months** prior to Visit 1 (Screening) or anticipate requiring penetrating intraocular surgery during the study.
12. Have had corneal refractive surgery (e.g. Lasik) or corneal transplantation (full thickness, anterior or posterior).
13. Have had eyelid surgery within **6 months** prior to Visit 1 (Screening) or anticipate requiring eyelid surgery during the study.
14. Have congenitally absent lacrimal glands or meibomian glands.
15. Have had laser trabeculoplasty or anticipate requiring laser trabeculoplasty.



16. Have had cauterization of the punctum or have had punctal plugs (silicone or collagen) inserted or removed less than **3 months** prior to Visit 1 (Screening) or planned during the study.

**NOTE:** If subject starts the study with punctal plugs, they must remain in place for the duration of the study and must be replaced if inadvertently removed.

17. Have a diagnosis of:

- a. Ongoing ocular infection
- b. Moderate to severe pinguecula or pterygia
- c. Stevens-Johnson Syndrome
- d. Significant conjunctival scarring
- e. Significant anterior blepharitis
- f. Severe/serious ocular condition that in the judgment of the investigator could confound study assessments or limit compliance.
- g. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance.

18. Have corneal fluorescein staining with diffuse confluent staining more than 33% of area (focal confluent staining is acceptable), or over 5 filaments or epithelial defects.

19. Have a history of herpetic keratitis.

20. [REDACTED]
- [REDACTED]
  - [REDACTED]
  - [REDACTED]

21. Have a history of ocular allergies, which, in the judgment of the investigator, are likely to have an acute increase in severity due to the expected timing of exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.

22. Have been exposed to an investigational product within **30 days** prior to Visit 1 (Screening).

23. Be an employee of the practice that is involved in the management, administration, or support of this study or be an immediate family member of the same.

24. Have a documented history of alcohol and/or drug abuse.

25. In the opinion of the Investigator or study coordinator, be unwilling or unable to comply with the study protocol or unable to successfully instill eye drops.

<p>26. Have used any marijuana products for 72 hours prior to Visit 1 (Screening) and for the duration of the study.</p> <p>27. Have been randomized for participation in KPI-121-C-006 (STRIDE 1) or KPI-121-C-007 (STRIDE 2).</p>
<p><b>Investigational product, dosage and mode of administration:</b> KPI-121 0.25% ophthalmic suspension</p>
<p><b>Dosage and duration of treatment:</b> 1 to 2 drops of investigational product will be instilled in each eye four times per day (QID) for approximately 14 days.</p>
<p><b>Reference therapy (Comparator), dosage and mode of administration:</b> KPI-121 0.25% ophthalmic vehicle will be supplied as investigational product.</p>
<p><b>Efficacy assessments:</b></p> <ul style="list-style-type: none"> <li>• Subject-rated assessment of ocular discomfort [REDACTED]</li> <li>• [REDACTED] assessment of bulbar conjunctival hyperemia</li> <li>• [REDACTED]</li> <li>• [REDACTED] corneal fluorescein staining</li> <li>• Subject-rated assessment of eye dryness</li> </ul> <p><b>Safety assessments:</b></p> <ul style="list-style-type: none"> <li>• Assessment of adverse events (AEs)</li> <li>• Slit lamp biomicroscopy</li> <li>• IOP measurement</li> <li>• BCVA</li> <li>• Dilated Ophthalmoscopy</li> <li>• Pregnancy screen (performed only at Visits 1 and 4)</li> </ul> <p><b>Statistical methods:</b></p> <p>All primary efficacy endpoint comparisons will be performed between the KPI-121 0.25% ophthalmic suspension group and the vehicle group [REDACTED]. The specific details of endpoint testing will be elaborated in the Statistical Analysis Plan (SAP).</p> <p><b>Primary Efficacy Analyses:</b></p> <p>The trial will have 2 primary endpoints [REDACTED] [REDACTED]:</p> <ol style="list-style-type: none"> <li>1. Change in ODS scores in the ITT population [REDACTED] [REDACTED].</li> </ol>

2. Change in ODS scores in the ITT subgroup with more severe baseline ocular discomfort

**Secondary Efficacy Analyses:**

Secondary efficacy endpoint comparisons will be performed between KPI-121 0.25% ophthalmic suspension group and the vehicle group if the null hypotheses for primary endpoints are rejected. The secondary endpoints testing will be:

1. Change from baseline (Day 1) in bulbar conjunctival hyperemia scores in the ITT population at Visit 4 (Day 15 + 2 days)
2. Change from baseline (Day 1) in bulbar conjunctival hyperemia scores in the ITT population at Visit 4 (Day 15 + 2 days)
3. Change in ODS scores in the ITT population
4. Change from baseline (Day 1) in corneal fluorescein staining scores in the ITT population at Visit 4 (Day 15 + 2 days) in the study eye.
5. Change in ODS scores in the ITT population

**Exploratory Efficacy Analyses:**

Exploratory efficacy endpoints will be evaluated.

### 3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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#### 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 2: Abbreviations and Specialist Terms**

Abbreviation or Specialist Term	Explanation
AR	Adverse Reaction
AE	Adverse Event
BCVA	Best Corrected Visual Acuity
°C	Degrees Celsius
CCLRU	Cornea and Contact Lens Research Unit
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ID	Identification
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
IWRS	Interactive Web Response System

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
KCS	Keratoconjunctivitis sicca
KPI	Kala Pharmaceuticals, Inc.
LE	Loteprednol etabonate
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
MPP	Mucus Penetrating Particles
NDA	New Drug Application
NEI	National Eye Institute
ODS	Ocular Discomfort Severity
QID	Four Times Daily
SAE	Serious Adverse Event
	
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
TNF	Tumor Necrosis Factor
UPT	Urine Pregnancy Test
US	United States of America
WOCBP	Women of Child Bearing Potential
w/v	Weight to Volume

## 5. INTRODUCTION

It is estimated that dry eye disease affects approximately 33 million people in the United States based on an estimated prevalence of 14.5% described in The Beaver Dam Offspring Study, a major epidemiological study published in 2014 in the American Journal of Ophthalmology (Paulsen, 2014). Dry eye disease, also called keratoconjunctivitis sicca (KCS) is characterized by several symptoms of ocular discomfort, including but not limited to dry eye sensation, foreign body sensation, irritation, burning, tearing, ocular pain, and itching. Subjects with dry eye disease may experience significant ocular discomfort and reduced visual function, thus resulting in a decreased quality of life or work productivity. Current treatment of dry eye disease generally begins with artificial tear replacement and then expands to include topical anti-inflammatory therapy and punctal occlusion. Three anti-inflammatory therapies for dry eye disease are currently approved by the FDA, and all are intended to be long-term treatments for dry eye disease: cyclosporine ophthalmic solution (Restasis<sup>®</sup>, Allergan; Cequa<sup>™</sup>, Sun Ophthalmics) and lifitegrast (Xiidra<sup>®</sup>; Shire). Cyclosporine has shown effectiveness in increasing tear volume in dry eye patients; however, it is not effective in subjects with punctal plugs or those already being treated with anti-inflammatory ophthalmic solutions (DEWS Report, 2007), it produces adverse reactions in a significant percentage of patients (eg, ocular irritation upon instillation, slow onset of response, and limited efficacy), and it may take several weeks to produce a therapeutic effect and up to 6 months for maximal effectiveness (Pflugfelder, 2004). Lifitegrast inhibits an integrin, lymphocyte function-associated antigen 1 (LFA-1) from binding to intercellular adhesion molecule 1 (ICAM-1), which down-regulates inflammation mediated by T lymphocytes; however, the exact mechanism of action of lifitegrast in dry eye disease is not known. The most common side effects of lifitegrast reported in 5% to 25% of subjects are instillation site irritation, dysgeusia (unusual taste sensation), and reduced visual acuity (Xiidra package insert, 2016).

Inflammation has a prominent role in the development and proliferation of dry eye disease. Factors adversely affecting tear film stability and osmolarity can initiate an inflammatory cascade that leads to the development of a self-perpetuating inflammatory cycle. Topical corticosteroids are used to treat an array of ocular conditions that have an inflammatory component and are generally indicated for treatment of steroid-responsive inflammatory conditions of the conjunctiva, cornea, and anterior segment.

LE is an ester corticosteroid that is rapidly metabolized to inactive metabolites and has been reported to have fewer side effects than traditional glucocorticosteroids. LE was approved by FDA in 1998 under New Drug Application (NDA) 20-583 (Lotemax<sup>®</sup>; Bausch & Lomb). Lotemax has gained wide acceptance by ophthalmologists for use in the treatment of ocular inflammation.

Kala Pharmaceuticals, Inc. (KPI) has developed an improved formulation of LE, designated KPI-121, using a proprietary technology known as Mucus Penetrating Particles (MPP). MPP technology utilizes submicron drug particles formulated to enhance penetration through the mucous layer of the tear film. KPI-121 is an aqueous suspension of submicron particles of LE formulated with excipients present in other FDA-approved ophthalmic drug products. Preclinical studies have shown improved pharmacokinetics for KPI-121 compared to Lotemax, with prolonged drug presence on the ocular surface and increased drug penetration into ocular tissues. This improved pharmacokinetic profile has the potential to reduce dosing strength of LE as compared to Lotemax.

Kala Pharmaceuticals, Inc. intends to develop KPI-121 for the treatment of dry eye disease. In previously conducted clinical trials (one phase 2 and two phase 3), the safety profile of KPI-121 in subjects with dry eye disease was shown to be favorable. Study KPI-121-C-011 will evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension in subjects with dry eye disease. Additional information about KPI-121, including nonclinical pharmacology study results, and potential risks and benefits to human subjects, are found in the Investigator's Brochure.

## **6. TRIAL OBJECTIVES AND PURPOSE**

### **6.1. Primary Objective**

The primary objective of the study is to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects who have a documented clinical diagnosis of dry eye disease.

## 7. INVESTIGATIONAL PLAN

### 7.1. Overall Study Design

This is a Phase 3, multicenter, double-masked, randomized, vehicle-controlled, parallel-group study designed to evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension in treating the signs and symptoms of dry eye disease.

This study will include up to 4 clinic visits, including 2 weeks of single-masked vehicle in Stage 1 followed by approximately 14 days of investigational product dosing (KPI-121 0.25% ophthalmic suspension or vehicle in Stage 2).

Approximately 3200 subjects at approximately 80 centers located in the United States (US) will be screened at Visit 1 (Screening). Subjects meeting eligibility criteria at this visit will enter a 14-day Stage 1 period of QID dosing with single masked vehicle. At Visit 2 (Day 1/Randomization), approximately 900 subjects who continue to meet eligibility criteria will be randomized in an approximate 1:1 ratio to either KPI-121 0.25% ophthalmic suspension or vehicle dosed QID. Subjects will be allocated in an approximate 1:1 ratio at each site.

Study qualification criteria will be entered into the Interactive Web Response System (IWRS) for stratification at randomization. Other randomization and stratification allocation criteria will be applied as elaborated in the data management plan. Randomization numbers will be automatically assigned to each subject as they are entered into the IWRS based on stratification criteria.

To minimize bias, investigational product allocation (KPI-121 0.25% ophthalmic suspension versus vehicle) will be randomized and masked to the Sponsor, subjects, and the investigative staff with the exception of a dosing coordinator. The dosing coordinator will be responsible for dispensing and retrieving investigational product to/from subjects, instructing subjects regarding dosing of the investigational product, addressing study subjects' questions regarding investigational product, [REDACTED]. As a consequence of these interactions, the dosing coordinator has the potential for being unmasked to the study treatment for each subject. The randomization schedule will be generated by the randomization statistician (who is not on the project team) or designee and maintained in a secure and limited-access location separate from the study Investigator and members of the project team.

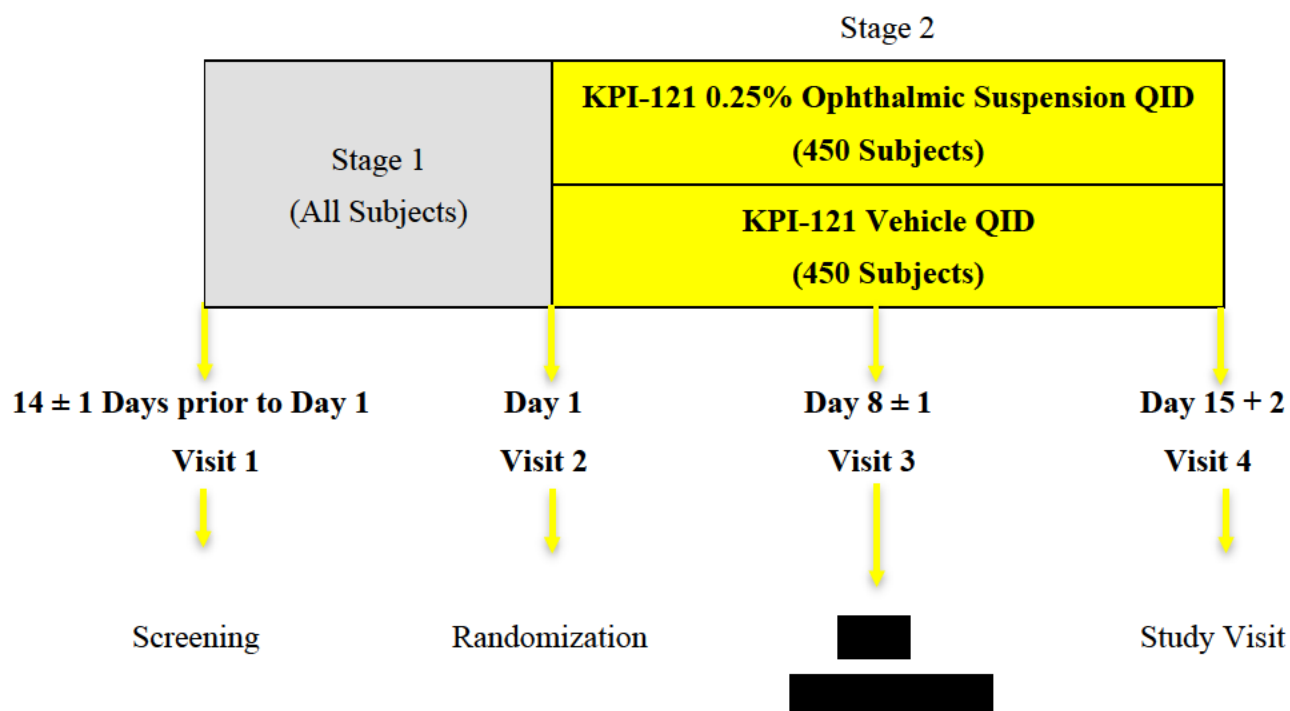
The "study eye" that is used for analyses will be determined according to the algorithm detailed in the final Statistical Analysis Plan.

Subjects will return at Visit 3 (Days  $8 \pm 1$  day) to [REDACTED] evaluate ocular discomfort and assess concomitant medication use and adverse events. Subjects

will return to the clinic for complete study evaluation and be released from the study at Visit 4 (Day 15 + 2 days).

Trial assessments will be performed according to the flowchart in Appendix 1 and assessed according to the standard procedures/scales as described in Appendix 2-12.

**Figure 1: Study Schematic**



## 7.2. Number of Subjects

Approximately 3200 subjects who are diagnosed with dry eye disease will be screened for this study. Approximately 900 of these subjects will be randomized to either KPI-121 0.25% ophthalmic suspension or vehicle.

## 7.3. Treatment Assignment

Subjects will be randomized to 1 of 2 study arms in an approximate 1:1 ratio, allocated at each investigational site. The study arms are: 1) KPI-121 0.25% ophthalmic suspension administered as 1-2 drops in each eye QID for approximately 14 days and 2) vehicle administered as 1-2 drops in each eye QID for approximately 14 days.

Furthermore, subjects will be assigned to a study arm based on the stratification of:

- Ocular discomfort severity scores [redacted] (low) and [redacted] (high) based on the subject's scoring of ocular discomfort severity [redacted].

The IWRS will assign masked study kit numbers. Bottles of investigational product will be dispensed at designated visits based on the subject's randomization. The Sponsor, Investigators, study staff, and subject will be masked during the randomization process and through the remainder of the study.

## **7.4. Visit Description**

### **7.4.1. Visit 1: 14 ± 1 Days Prior to Day 1 – Screening**

After obtaining written informed consent and HIPAA authorization, site staff will perform/assess the following in the order suggested below. Each subject that is screened will be assigned a Subject Identification (ID) consisting of a 5-digit Investigator number plus a 3-digit Subject number. The Subject ID will be used as the primary subject identifier for the duration of the study.

- Subject-rated assessment of ocular discomfort as graded by the subject [REDACTED]
- Significant non-ocular and significant ocular medical history
- Concomitant medication usage and medications taken during the 6 months prior to screening
- Inclusion/exclusion criteria
- Urine pregnancy test (UPT) for WOCBP
- BCVA
- [REDACTED] assessment of bulbar conjunctival hyperemia
- Slit Lamp Biomicroscopy
- Corneal fluorescein staining
- Unanesthetized Schirmer Test evaluation
- IOP measurement
- Dilated Ophthalmoscopy
- Single-masked, investigational product instillation
- AE Assessment



- Dispense single masked, investigational product and instructions for administration
  - The first dose of single-masked investigational product will be administered in the clinic under the supervision of a designated dosing coordinator. This dosing coordinator, who is not responsible for study assessments, will also be required to dispense and retrieve investigational product to/from the subjects, provide instruction to the subjects regarding dosing of the investigational product, address study subjects' questions regarding the investigational product, [REDACTED]. Prior to administration of investigational product, subjects will be instructed regarding proper method for instillation of investigational product including but not limited to shaking investigational product bottle prior to each instillation. Since subjects will receive 1 dose of investigational product in the clinic, they will self-administer at most 3 additional doses of investigational product on the first day.

- [REDACTED]

**Instructions to subject:**

- Dose single-masked Stage 1 investigational product as instructed
- [REDACTED]
- [REDACTED]
- Return for Visit 2 scheduled in  $14 \pm 1$  days.

**7.4.2. Visit 2: Day 1 – Randomization**

The randomization visit will occur  $14 \pm 1$  days after Visit 1 (Screening). This visit, the first visit of Stage 2, should be scheduled in the morning (if possible) to allow for administration of QID dosing of investigational product during the day for eligible subjects.

Eligible subjects who continue to meet the eligibility criteria (Section 8) will continue in the study. The site staff will perform/assess the following in the order suggested below:

- Subject-rated assessment of eye dryness
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit and a status review of any ongoing AEs
- [REDACTED]

- Used and unused single-masked Stage 1 investigational product collected, counted, and compliance assessed [REDACTED]
- [REDACTED] assessment of bulbar conjunctival hyperemia
- [REDACTED]
- BCVA
- Slit Lamp Biomicroscopy
- Corneal fluorescein staining
- IOP measurement
- Upon verification of study eligibility, randomization of appropriate subjects to receive QID dosing of either KPI-121 0.25% ophthalmic suspension or vehicle.

The following will be performed for all randomized subjects:

- Instillation of randomized investigational product
- AE Assessment
- Dispensing of double-masked, investigational product (1 bottle) and instructions for administration

The first dose of double-masked investigational product will be administered in the clinic under the supervision of a designated dosing coordinator. This dosing coordinator, who is not responsible for study assessments, will also be required to dispense and retrieve investigational product to/from the subjects, provide instruction to the subjects regarding dosing of the investigational product, address study subjects' questions regarding the investigational product, [REDACTED]. Prior to administration of investigational product, subjects will be instructed regarding proper method for instillation of their assigned investigational product including but not limited to shaking investigational product bottle prior to each instillation. Since subjects will receive 1 dose of investigational product in the clinic, they will self-administer at most 3 additional doses of investigational product on the first day. Any Stage 1 doses taken on the morning of Visit 2 should be counted into the total 4 doses for the day.

- [REDACTED]

**Instructions to subject:**

- Dose investigational product as instructed

- Complete dosing information [REDACTED]
- Complete ocular discomfort assessments [REDACTED]
- Return for Visit 3 scheduled on Day 8  $\pm$  1 day.

**7.4.3. Visit 3: Day 8  $\pm$  1 day – [REDACTED]**

This visit will occur on Day 8  $\pm$  1 day as calculated from Visit 2: Day 1, and the following evaluations will be performed:

- Subject-rated assessment of eye dryness
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit and a status review of any ongoing AEs
- [REDACTED]

**Instructions to subject:**

- Dose investigational product as instructed
- [REDACTED]
- [REDACTED]
- Return for Visit 4 scheduled on Day 15 + 2 days.

**7.4.4. Visit 4: Day 15 + 2 days – End of Study Visit**

The end-of-investigational-product-use visit will occur on Day 15 +2 days as calculated from Visit 2: Day 1. The site staff will perform/assess the following in the order suggested below:

- Subject-rated assessment of eye dryness
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit and a status review of any ongoing AEs
- [REDACTED]
- Used and unused double-masked investigational product collected, counted, and compliance assessed [REDACTED]
- [REDACTED] assessment of bulbar conjunctival hyperemia

- [REDACTED]
- BCVA
- Slit Lamp Biomicroscopy
- Corneal fluorescein staining
- IOP measurement
- Dilated ophthalmoscopy
- UPT for WOCBP
- Release of subject from the study

#### 7.4.5. **Unscheduled Visit**

Any visits or procedures performed beyond those specified within the protocol must be documented in the Unscheduled Visit pages of the electronic case report form (eCRF).

Unscheduled visits may include but are not limited to reporting adverse events (AEs), changes in concomitant medications, or ophthalmic assessments as deemed appropriate by an appropriately qualified physician. If the subject is discontinuing study participation at the unscheduled visit, the eCRFs for Visit 4 should be completed rather than the eCRFs for an Unscheduled Visit.

#### 7.4.6. **Early Termination Visit**

In the event of termination prior to Visit 4, every attempt will be made to ensure that **all Visit 4 assessments are performed**. If this is not feasible, at least the following should be performed/assessed:

- Subject-rated assessment of eye dryness
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit and a status review of any ongoing AEs
- Used and unused investigational product collected and compliance assessed [REDACTED]  
[REDACTED].
- Bulbar conjunctival hyperemia [REDACTED]
- BCVA
- Slit lamp biomicroscopy

- IOP measurement
- UPT for WOCBP

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

### 8.1. Subject Inclusion Criteria

Visit 1 (Screening) and Visit 2 (Day 1), individuals of either gender or any race will be eligible for study participation if they:

1. Provide written informed consent and HIPAA authorization prior to any study-related procedures.
2. Are 18 years of age or older.
3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study, including:
  - a. Single-masked investigational product use compliance of at least 80% during the final week of Stage 1 [REDACTED]
  - b. [REDACTED]
4. Have a documented clinical diagnosis of dry eye disease in both eyes.
5. Have ongoing dry eye disease as defined by the following criteria in the **same eye or both eyes**:
  - a. Total corneal fluorescein staining (CFS) score [REDACTED] [National Eye Institute (NEI) scale] [REDACTED] **at both Visit 1 (Screening) and Visit 2 (Day 1)** AND
  - b. [REDACTED] assessment of bulbar conjunctival hyperemia [REDACTED] [Cornea and Contact Lens Research Unit (CCLRU) scale] **at both Visit 1 (Screening) and Visit 2 (Day 1)** [REDACTED] AND
  - c. Unanesthetized Schirmer Test score of [REDACTED] **at Visit 1 (Screening)** in the same eye as qualified for 5b criterion above AND
  - d. [REDACTED] ocular discomfort severity (ODS) [REDACTED] **at Visit 1 (Screening)** AND
  - e. [REDACTED] ODS score [REDACTED] AND
  - f. [REDACTED]
6. Have normal lid anatomy.

7. Are WOCBP who are not pregnant or lactating and not sexually active (i.e., abstinent) for 14 days prior to Visit 1 (Screening) and willing to remain so through 30 days following Visit 4 or the last administration of the investigational product or until completion of the subject's first menstrual cycle following the last administration of the investigational product, whichever period of time is longer. Alternatively, WOCBP who are not abstinent must have been using 1 of the following acceptable methods of birth control for the times specified:

- a. IUD in place for at least **3 months** prior to Visit 1 (Screening) and continuing through Visit 4 or last administration of investigational product or until completion of the subject's first menstrual cycle following last administration of the investigational product, whichever period of time is longer.
- b. Barrier method (condom or diaphragm) with spermicide for at least **3 months** prior to Visit 1 (Screening) and continuing through Visit 4 or last administration of the investigational product or until completion of the subject's first menstrual cycle following last administration of the investigational product, whichever period of time is longer.
- c. Stable hormonal contraceptive for at least **3 months** prior to Visit 1 (Screening) and continuing through Visit 4 or last administration of the investigational product or until completion of the subject's first menstrual cycle following administration of the investigational product, whichever period of time is longer.

**NOTE:** For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following administration of the investigational product is not applicable as females receiving this form of contraception will not have menses.

- d. In a monogamous relationship with a surgically sterilized (i.e., vasectomized) partner at least **6 months** prior to Visit 1 (Screening) through Visit 4 or last administration of the investigational product or until completion of the subject's first menstrual cycle following administration of the investigational product, whichever period of time is longer.
8. Are postmenopausal women (i.e., no menstrual cycle for at least one year prior to Visit 1 (Screening)) or are women who have undergone 1 of the following sterilization procedures at least 6 months prior to Visit 1 (Screening):
- a. Bilateral tubal ligation
  - b. Hysterectomy
  - c. Hysterectomy with unilateral or bilateral oophorectomy.
  - d. Bilateral oophorectomy

## 8.2. Subject Exclusion Criteria

In order for subjects to be eligible at Visit 1 (Screening) and Visit 2 (Day 1) they may not:

1. Have a known hypersensitivity or contraindication to the investigational product(s) or their components.
2. Have used any of the following medications or had any of the following procedures within **30 days** prior to Visit 1 (Screening) or for the duration of the study:
  - a. Ocular, inhaled or intranasal corticosteroids
  - b. Ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of  $\leq 81$  mg/day of acetylsalicylic acid (ASA or aspirin)
  - c. Topical ocular antibiotics
  - d. Topical ocular antihistamines or mast cell stabilizers
  - e. Oral antihistamines
  - f. Topical or nasal vasoconstrictors
  - g. Autologous serum tear preparations
  - h. Lipiflow treatment
  - i. TruTear treatment
  - j. Blephex treatment
3. Have used any of the following medications within **60 days** prior to Visit 1 (Screening) or for the duration of the study:
  - a. Topical cyclosporine (Restasis®)
  - b. Topical lifitegrast
  - c. Any form of topical loteprednol etabonate (LE)
4. Have altered oral dosing of the following within **30 days** prior to Visit 1 (Screening) or anticipate alteration of dosing during the study:
  - a. Tetracycline compounds (e.g., tetracycline, doxycycline, or minocycline)
  - b. Omega-3 or Omega-6 supplements
5. Have altered dosing of the following medications within **6 months** prior to Visit 1 (Screening) or anticipate alteration of dosing during the study:
  - a. Anticholinergics
  - b. Anticonvulsants (e.g., topiramate)
  - c. Antidepressants



- d. Isotretinoin
  - e. Systemic immunosuppressive agents including oral corticosteroids at a dose of prednisone  $\leq 11$  mg/day or equivalent.  
**NOTE:** Oral corticosteroid use at a dose of prednisone  $>11$  mg/day or equivalent is excluded.
- 6. Be unwilling to abstain from the use of any topical ophthalmic medications **at Visit 1 (Screening)** and for the duration of the study, including:
    - a. Eyelash growth medications, including both prescription and over-the-counter
    - b. Eye drops, gels, ointments, or artificial tears
  - 7. Be unwilling to abstain from the use of TNF-blocking agents (e.g. etanercept, adalimumab, infliximab) **at Visit 1 (Screening)** and for the duration of the study.
  - 8. Be currently receiving treatment for glaucoma **at Visit 1 (Screening)** or for the duration of the study and/or have history of or current glaucoma, or an IOP over 21mmHg **at Visit 1 (Screening) or Visit 2 (Day 1)**.
  - 9. Be unwilling to abstain from wearing contact lenses for **14 days** prior to Visit 1 (Screening) and for the duration of the study.
  - 10. Be monocular or have a BCVA of  $+1.0$  logMAR or worse as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS).
  - 11. Have had penetrating intraocular surgery within **3 months** prior to Visit 1 (Screening) or anticipate requiring penetrating intraocular surgery during the study.
  - 12. Have had corneal refractive surgery (e.g. Lasik) or corneal transplantation (full thickness, anterior or posterior).
  - 13. Have had eyelid surgery within **6 months** prior to Visit 1 (Screening) or anticipate requiring eyelid surgery during the study.
  - 14. Have congenitally absent lacrimal glands or meibomian glands.
  - 15. Have had laser trabeculoplasty or anticipate requiring laser trabeculoplasty.
  - 16. Have had cauterization of the punctum or have had punctal plugs (silicone or collagen) inserted or removed less than **3 months** prior to Visit 1 (Screening) or planned during the study.  
**NOTE:** If subject starts the study with punctal plugs, they must remain in place for the duration of the study and must be replaced if inadvertently removed.
  - 17. Have a diagnosis of:
    - a. Ongoing ocular infection
    - b. Moderate to severe pinguecula or pterygia

- c. Stevens-Johnson Syndrome
  - d. Significant conjunctival scarring
  - e. Significant anterior blepharitis
  - f. Severe/serious ocular condition that in the judgment of the investigator could confound study assessments or limit compliance.
  - g. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance.
18. Have Corneal Fluorescein Staining with diffuse confluent staining more than 33% of area (focal confluent staining is acceptable), or over 5 filaments or epithelial defects.
19. Have a history of herpetic keratitis.
20. [REDACTED]
21. Have a history of ocular allergies, which, in the judgment of the investigator, are likely to have an acute increase in severity due to the expected timing of exposure to the allergen to which the subject is sensitive. Subjects sensitive to seasonal allergens that are not expected to be present during the study are permitted.
22. Have been exposed to an investigational product within **30 days** prior to Visit 1 (Screening).
23. Be an employee of the practice that is involved in the management, administration, or support of this study or be an immediate family member of the same.
24. Have a documented history of alcohol and/or drug abuse.
25. In the opinion of the Investigator or study coordinator, be unwilling or unable to comply with the study protocol or unable to successfully instill eye drops.
26. Have used marijuana products for 72 hours prior to Visit 1 (Screening) and for the duration of the study.
27. Have been randomized for participation in KPI-121-C-006 (STRIDE 1) or KPI-121-C-007 (STRIDE 2).

### **8.3. Subject Withdrawal and Study Termination Criteria**

Any subject who wishes to may withdraw from the investigational product use or from participation in the study of his or her own accord for any reason is entitled to do so without obligation. The Investigator may also withdraw any subject from the investigational product use or from study participation, if deemed necessary.

Investigational product use may be discontinued and any subject may be discontinued from study participation at any time during the study at the discretion of the Investigator or the Sponsor for any reason including but not limited to:

1. Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
3. Subject's decision to withdraw.
4. Any woman who becomes pregnant while participating in the study. Information on the pregnancy and outcome will be requested.
5. Subject's failure to comply with protocol requirements or study related procedures.
6. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

In the event study discontinuation of a randomized subject is necessary, the Investigator should make every attempt to have subject complete Visit 4 assessments as possible. The reason for premature discontinuation should be entered onto the eCRF and recorded in the subject chart.

Subjects who withdraw from the study will not be replaced.

Additionally, the trial or parts of the trial may be discontinued by the Sponsor or at the recommendation of the Investigator after consultation with Kala Pharmaceuticals, Inc. This may be based on a significant number of AEs of a similar nature that warrant such action.

## 9. TREATMENT OF SUBJECTS

### 9.1. Description of Investigational product

The compositions of KPI-121 0.25% and its matching placebo (vehicle) are listed in Table 3 and Table 4, respectively.

**TABLE 3: COMPOSITION OF KPI-121 0.25% (W/V) INVESTIGATIONAL PRODUCT**

Ingredient	Function	Concentration (% w/v)
Loteprednol etabonate	Active pharmaceutical ingredient	0.25
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

**TABLE 4: COMPOSITION OF PLACEBO (VEHICLE)**

Ingredient	Function	Concentration (% w/v)
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

### 9.2. Concomitant Medications

All medications that the subject has taken 6 months prior to Visit 1 (Screening) and through Visit 4 or discontinuation from the study will be recorded in the eCRF and the subject chart. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an AE or as a rescue medication will be recorded for each medication.

Medications and/or procedures not specifically excluded in the list below may be taken and/or conducted as necessary.

At **Visit 1 (Screening)** and for the duration of the study:

- Any topical ophthalmic medications including eyelash growth medications (including both prescription and over-the-counter), eye drops, gels, ointments, or artificial tears
- TNF-blocking agents (e.g. etanercept, adalimumab, infliximab)
- Treatment for glaucoma

Within **30 days** prior to Visit 1 (Screening) and for the duration of the study:

- Ocular, inhaled, or intranasal corticosteroids
- Ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of  $\leq 81$  mg/day of acetylsalicylic acid (ASA or aspirin)
- Topical ocular antibiotics
- Topical ocular antihistamines or mast cell stabilizers
- Oral antihistamines
- Topical or nasal vasoconstrictors
- Other investigational products
- Autologous serum tear preparations

Within **60 days** prior to Visit 1 (Screening) and for the duration of the study:

- Topical cyclosporine (Restasis®)
- Topical lifitegrast
- Any form of topical LE

Within **30 days** prior to the screening visit (Visit 1) alteration to the dose or anticipated alterations to the dose of the following are disallowed:

- Tetracycline compounds (tetracycline, doxycycline, or minocycline)
- Omega-3 or Omega-6 supplements

Within **6 months** prior to the screening visit (Visit 1) alterations to the dose or anticipated alterations to the dose of the following are disallowed:

- Anticholinergics
- Anticonvulsants (e.g., topiramate)
- Antidepressants
- Isotretinoin

- Systemic immunosuppressive agents including oral corticosteroids at a dose of prednisone  $\leq 11$  mg/day or equivalent.

**NOTE:** Oral corticosteroid use at a dose of prednisone  $>11$  mg/day or equivalent is excluded.

Any subjects not responding adequately to the study medication may be rescued and placed on alternate therapy at the Investigator's discretion at any time. The choice of rescue medication is at the Investigator's discretion. Any subject placed on rescue therapy will discontinue use of the study medication and continue study participation through Visit 4.

The need for rescue therapy will not be considered an AE. Rescued subjects experiencing an AE at the time of rescue will be followed through stabilization or resolution of the AE or the end of the study (whichever comes last). Rescued subjects should not be withdrawn from the study, but rather followed to resolution of signs and symptoms or until the Investigator has deemed the subject is stable.

### 9.3. Treatment Compliance


Compliance will be assessed by [REDACTED] investigational product accountability records [REDACTED]. The site will document this [REDACTED] along with verification of the numbers of used and unused investigational product bottles. The numbers of missed doses as assessed at each clinic visit should be documented in the eCRF.

### 9.4. Randomization and Masking

The Sponsor, the project teams at the designated Contract Research Organizations (CROs), and investigative staff responsible for assessments of study endpoints will be masked to investigational product assignments. A dosing coordinator, who is not responsible for study assessments, will be required to dispense and retrieve investigational product to the subjects. In case of medical emergency, or occurrence of an SAE, the randomization code may be unmasked and made available to the Investigator, Sponsor, and/or other personnel involved in the monitoring or conduct of this study. In the absence of medical need, the randomization code will not be available to the above individuals until after the study is completed and the database is locked.

In the event of a medical need, the Investigator will treat each subject as needed. Since there is no specific antidote to KPI-121, immediate emergency unmasking is not necessary. If the Investigator feels it is necessary to unmask a subject's assignment after an emergency situation, the Investigator may call the medical monitor and notify the Sponsor. The investigational product assignment will be revealed on a subject-by-subject basis with the approval of the medical monitor and Sponsor, thus leaving the masking of the remaining subjects intact.

A randomization code will be computer-generated by Kala Pharmaceuticals, Inc. or designee. Randomization team members will work independently of other team members. Study personnel involved in subject assessment (i.e., not the dosing coordinator), study subjects, the Sponsor, and project teams at the CROs involved in the study will be masked to investigational product assignments.



## **10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT**

### **10.1. Investigational product**

KPI-121 0.25% ophthalmic suspension contains submicron particles of LE suspended in a formulation consisting of excipients that have been used in other FDA-approved ophthalmic products.

KPI-121 0.25% drug product will be supplied as a suspension in opaque dropper bottles. KPI-121 0.25% ophthalmic suspension is a sterile, aqueous, submicron suspension of LE and will be supplied in a 10 mL, white, low-density polyethylene dropper bottle with a translucent, controlled-drop linear low-density polyethylene tip, a pink high-density polyethylene cap, and a white, low-density polyethylene, tamper-evident overcap. Each bottle contains 8.2 mL (nominal fill) of drug product.

Subjects randomized to the vehicle control arm will receive the same bottles containing all components at the concentrations used in the KPI-121 0.25% ophthalmic suspension with the exception of the active component, LE.

### **10.2. Investigational product Packaging and Labeling**

The Stage 1 investigational product will be 1 bottle of single-masked, investigational product (vehicle) from a common site level supply which will be provided to the subject after qualifying for Stage 1. The bottle labels for the single-masked period contain the following information: Sponsor name, protocol number, lot number, unique identifying number, storage temperature, and required statement(s) per the FDA requirements.

The randomized investigational product kit will consist of a box containing 2 dropper bottles of investigational product. At Day 1, eligible subjects will receive 1 bottle of investigational product. The second bottle will be retained at the site and provided to the subject in the event the subject needs additional investigational product during the treatment period. The box label and dropper bottle labels will contain the following information: Sponsor name, protocol and kit number, storage temperature, and required statement(s) per the FDA requirements.

### **10.3. Investigational product Storage**

All investigational products will be stored at the site upright in a secure area, with limited access, at 15-25°C/59 -77°F.

### **10.4. Investigational product Preparation**

Subjects will be instructed to shake the investigational product bottle for 2 to 3 seconds prior to each instillation.



### **10.5. Administration**

At Visits 1 and 2, when subjects receive the first dose in the clinic, that dose will count as 1 of their 4 (QID) daily doses. Subjects will then self-administer at most 3 additional doses of investigational product during the remainder of that day to complete QID dosing. All visits should be scheduled in the morning to allow subjects to receive a full day of QID dosing. Any Stage 1 doses taken on the morning of Visit 2 should be counted into the total 4 doses for the day.

Subjects will be asked to instill 1 dose upon awakening and then 3 subsequent doses approximately 4 hours after their previous dose. The 4 doses will be described as “Morning Dose,” “Mid-Morning Dose,” “Afternoon Dose,” and “Evening Dose.”

### **10.6. Investigational product Accountability**

Sponsor study monitors or designees will conduct accountability of investigational product (KPI-121 0.25% ophthalmic suspension or vehicle). Accountability will be ascertained by performing reconciliation between the amount of investigational product sent to the site and the amount used and unused at the time of reconciliation.

Clinical trial materials will be shipped to the investigational sites under sealed conditions. Investigational product shipment records will be verified by comparing the shipment inventory sheet to the actual quantity of investigational product received at the site. Accurate records of receipt and disposition of the investigational product (e.g., dates, quantity, subject number, dose dispensed, returned) must be maintained by the Investigator or his/her designee.

### **10.7. Investigational product Handling and Disposal**

At the end of the study, all study materials, including any unused investigational products (KPI-121 0.25% ophthalmic suspension or vehicle), as well as original containers (even if empty), will be returned to the drug-packaging vendor in accordance with Sponsor or designee’s Standard Operating Procedures (SOPs), following approval by the Sponsor. All returns of investigational product will be documented. The study monitor or designee will verify investigational product accountability. All investigational product accounting procedures must be completed before the study is considered complete.

## 11. ASSESSMENT OF EFFICACY

Efficacy assessments will be performed according to the schedule of events provided in Appendix 1 and include:

- Subject-rated assessment of ocular discomfort [REDACTED]  
[REDACTED]
- [REDACTED] bulbar conjunctival hyperemia
- [REDACTED]
- [REDACTED] corneal fluorescein staining
- Subject-rated assessment of eye dryness

## **12. ASSESSMENT OF SAFETY**

### **12.1. Safety Parameters**

An ophthalmic examination will be performed at all study visits, except at Visit 3, according to the schedule of events provided in Appendix 1. Safety parameters include:

- Assessments of AEs
- BCVA
- Slit lamp biomicroscopy
- Dilated ophthalmoscopy
- IOP measurement
- Pregnancy screen (performed only at Visits 1 and 4 on WOCBP)\*

\*All pregnancies are to be reported from the time informed consent is signed until Visit 4/End of study. Any report of pregnancy for any subject must be reported within 24 hours of site awareness to Kala or its delegate using the Pregnancy Report Form. The Pregnancy form should be faxed to [REDACTED] or emailed to [REDACTED]

Women who have a positive pregnancy test during the study will be withdrawn from the study treatment and, whenever possible, should complete all remaining study visits and assessments. 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 postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage, premature birth or congenital abnormality are considered SAEs. The SAE must be entered on the AE eCRF in EDC and the SAE fax cover letter completed then faxed to 1-[REDACTED] or emailed to [REDACTED]

### **12.2. Adverse and Serious Adverse Events**

#### **12.2.1. Definition of Adverse Events**

##### **12.2.1.1. Adverse Event (AE)**

Adverse Event (AE): Any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered drug related.

Adverse Reaction (AR): any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Suspected Adverse Reaction (SAR):

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. A SAR implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Unexpected: An AE or SAR is considered “unexpected” if it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator’s Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

Life-threatening: An AE or SAR is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **12.2.1.2. Serious Adverse Event (SAE)**

A **SERIOUS ADVERSE EVENT (SAE)** is any AE or suspected adverse reaction occurring at any dose that:

- Results in death.
- Is life-threatening.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Requires in subject hospitalization.
- Prolongs in subject hospitalization.
- Is a congenital anomaly/birth defect.
- Is a significant medical event (i.e., one that may jeopardize the subject or may require intervention to prevent one or more of the other outcomes listed above).

A **NON-SERIOUS ADVERSE EVENT** is any AE that does not meet the definitions for SAEs as described above.

Each AE will be classified as **SERIOUS or NON-SERIOUS** using the definitions provided above.

### **12.3. Relationship to Investigational product**

The **SEVERITY** of each AE will be classified as **MILD, MODERATE, or SEVERE**.

The Investigator will review each event and assess its **RELATIONSHIP** to use of investigational product (unrelated, unlikely, possibly, probably, definitely). The AE will be assessed using the following definitions:

**Unrelated:**

- Event occurring before dosing.
- Event or intercurrent illness due wholly to factors other than investigational product use.

**Unlikely:**

- Poor temporal relationship with investigational product use.
- Event easily explained by subject's clinical state or other factors.

**Possibly:**

- Reasonable temporal relationship with investigational product use.
- Event could be explained by subject's clinical state or other factors.

**Probably:**

- Reasonable temporal relationship with investigational product use.
- Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot easily be explained by subject's clinical state or other factors.

**Definitely:**

- Distinct temporal relationship with investigational product use.
- Known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot be explained by subject's clinical state or other factors.

## **12.4. Recording Adverse Events**

AEs will be monitored throughout the study (from the time of ICF signature through Visit 4) and will be recorded on the eCRF with the date and time of onset, date and time of resolution, severity, seriousness, causality (relationship to use of investigational product), treatment required, and the outcome.

To elicit AEs, simple questions with minimal suggestions or implications should be used as the initial questions at all evaluation points during the trial. For example:

How have you felt since your last assessment?

Have you had any health problems since your last assessment?

The severity of each AE should be categorized as mild, moderate, or severe.

The causality of use of investigational product in relation to the AE will be assessed by the Principal Investigator after careful medical consideration and categorized as unrelated, unlikely, possible, probable, or definite.

If an AE occurs, the Investigator will institute support and/or treat as deemed appropriate. If a non-SAE is unresolved at the time of the last day of the study, an effort will be made to follow up until the AE is resolved or stabilized, the subject is lost to follow-up, or there is some other resolution of the event. The Investigator should make every attempt to follow SAEs to resolution.

## **12.5. Reporting Adverse Events**

### **Serious Adverse Event Reporting**

It is the responsibility of the Investigators or their designees to report any event of this nature to the Sponsor or a designee within 24 hours of the event being brought to the Investigators' or their staffs' attention. It is also the responsibility of the Investigator to report all SAEs reported at their site to their Institutional Review Board (IRB), as required. The Investigator should make every attempt to follow all SAEs to resolution.

The following information should be provided when an SAE is reported to the Sponsor or designee:

1. Protocol Number
2. Site Number
3. Subject Number
4. Subject Demographic information, including:
  - Date of Birth
  - Sex
  - Race
5. Investigational product start date
6. Date of last dose of investigational product
7. Date investigational product reinitiated (if investigational product interrupted)
8. SAE information, including:
  - SAE term (diagnosis only; if known or serious signs/symptoms)
  - Description of SAE/narrative

- Date/time of onset
  - Severity
  - Outcome
  - Date/time of resolution or death (if duration < 24 hours)
  - Relationship to investigational product
  - Action taken with investigational product
9. Criteria for classifying the event as serious, including whether the SAE:
- Resulted in death.
  - Was life-threatening
  - Required inpatient hospitalization.
  - Prolonged inpatient hospitalization.
  - Resulted in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - Was a congenital anomaly/birth defect.
  - Important medical events that may not result in death, were not life-threatening, or did not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one 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 subject hospitalization, or the development of drug dependency or drug abuse.
10. Concomitant medications
11. Relevant history
12. Possible causes of SAE other than investigational product

13. Copy of AE page from the eCRF

**NOTE:** If an SAE occurs in any study involving KPI-121 0.25% ophthalmic suspension that is unexpected and is determined to be related or possibly related to investigational product, all sites will be notified by the Sponsor and each site should report it to its IRB.



### 13. STATISTICS

Continuous measures (e.g., age) will be summarized descriptively by the mean, standard deviation, median, minimum and maximum values. Categorical measures will be summarized by the number and percent of subjects.

#### 13.1. Subject Demographics, Disposition and Background variables

Subject disposition, demographic characteristics, and background variables will be summarized by study group.

#### 13.2. Analysis of Efficacy

##### 13.2.1. Primary Efficacy Analyses

The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all randomized subjects who received at least one dose of randomized investigational product. A subset of efficacy analyses will be examined for the Per Protocol (PP) population, the definition of which will be outlined in the Statistical Analysis Plan (SAP) and finalized prior to unmasking of study data pursuant to clinical data review. The specific details of endpoint testing will be elaborated in the SAP. If changes to the Statistical Analysis elaborated in the protocol are deemed necessary, those changes will be made prior to unmasking the study data and may only be elaborated in the Statistical Analysis Plan.

The trial will have 2 primary endpoints each tested at [REDACTED]:

1. Change in ODS scores in the ITT population [REDACTED]  
[REDACTED]
2. Change in ODS scores in the ITT subgroup with more severe baseline ocular discomfort [REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 13.2.2. Secondary Efficacy Analyses

Secondary efficacy endpoint comparisons will be performed between KPI-121 0.25% ophthalmic suspension group and the vehicle group [REDACTED] if the null hypotheses for the primary endpoints are rejected. The [REDACTED] secondary endpoints testing will be [REDACTED]:

1. Change from baseline (Day 1) in bulbar conjunctival hyperemia scores in the ITT population at Visit 4 (Day 15 + 2 days) [REDACTED] in the study eye [REDACTED].
2. Change from baseline (Day 1) in bulbar conjunctival hyperemia scores in the ITT population at Visit 4 (Day 15 + 2 days) [REDACTED].
3. Change in ODS scores in the ITT population [REDACTED].
4. Change from baseline (Day 1) in [REDACTED] corneal fluorescein staining scores in the ITT population at Visit 4 (Day 15 + 2 days) in the study eye.
5. Change in ODS scores in the ITT population [REDACTED].

### 13.2.3. Exploratory Efficacy Analyses

Exploratory efficacy endpoints will be evaluated.

### 13.3. Analysis of Safety

Analysis of safety data will be presented for all subjects in the Safety population (i.e., all randomized subjects receiving at least one dose of randomized investigational product and from whom at least one safety assessment is obtained after randomization). AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, most current version) and categorized by system organ class using preferred terms. AEs will be tabulated by study group with respect to their Severity and relationship to the investigational product. Ophthalmoscopy findings will be summarized descriptively. IOP measurements, BCVA and Biomicroscopy will be summarized as safety outcomes.

### 13.4. Sample Size Estimation

Ocular discomfort severity, Day 15, ITT: A sample size of 450 in each group will have > 99% power to detect an effect size of [REDACTED] using a 2-group t-test with a [REDACTED] 2-sided significance level.

Ocular discomfort severity, Day 15, Subgroup with [REDACTED] [REDACTED]: A sample size of 225 in each group will have 95% power to detect an effect size of [REDACTED] using a 2-group t-test with a [REDACTED] 2-sided significance level.

### **13.5. Level of Significance**

[REDACTED] Overall the Type I error rate is controlled at 0.05.

[REDACTED] All other reported  $p$ -values will be considered descriptive and hypothesis generating.

### **13.6. Procedure for Accounting for Missing, Unused or Spurious Data**

Any missing, unused, or spurious data will be noted in the final clinical study report. If more than 5% of data are missing, multiple imputation will be employed to analyze incomplete data sets under the assumption that missing data are, at worst, characterized as missing at random (MAR). Imputation will be carried out for the analysis of only the primary endpoints. The reasons for missing data will be recorded and the impact of these reasons and any treatment group imbalance on the assumption of MAR will be evaluated.

### **13.7. Procedure for Reporting Deviations from the Statistical Plan**

Any deviations from the statistical analysis plan will be described and a justification given in the final clinical study report.

## **14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

### **14.1. Study Monitoring**

The progress of the study will be monitored by on-site, written, e-mail, and telephone communications between personnel at the study center and the Sponsor (or designated monitor). The Investigator will allow Kala Pharmaceuticals, Inc. monitors or designee to inspect all CRFs; subject records (source documents); signed informed consent forms; HIPAA authorizations; records of investigational product receipt, storage, and disposition; and regulatory files related to the study.

### **14.2. Audits and Inspections**

Authorized representatives of Kala Pharmaceuticals, Inc, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Kala Pharmaceuticals, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Kala Pharmaceuticals, Inc immediately if contacted by a regulatory agency about an inspection.

### **14.3. Institutional Review Board (IRB)**

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

## **15. QUALITY CONTROL AND QUALITY ASSURANCE**

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Kala Pharmaceuticals, Inc. may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

## **16. ETHICS**

### **16.1. Ethics Review**

This protocol and the informed consent form must be approved by an appropriately constituted and qualified IRB and the approvals made available to the Sponsor or designee prior to the start of enrollment into the study based on these items. Materials used to recruit subjects will be approved by the appropriate IRB and the approvals made available to the Sponsor or designee prior to their use. In addition, the Investigator's Brochure should be submitted to the IRB. Written IRB approval must adequately identify the protocol and informed consent form. Copies of all approved materials, all correspondence with the IRB, and written approval from the IRB must be made available to the Sponsor (or designated monitor).

Any modification of study procedures or amendments to the protocol must be approved by the IRB prior to implementation. In the event that a modification or amendment is considered by the Investigator to be immediately necessary to ensure subject safety, the Investigator will promptly notify his or her IRB and the Sponsor.

Investigators will report all SAEs reported at their site to their IRB, as appropriate.

### **16.2. Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

### **16.3. Written Informed Consent**

Written informed consent will be obtained from each participant prior to any study-related procedures being performed [prior to or upon Visit 1 (Screening)]. A copy of the signed and dated informed consent document will be given to each subject. The original signed and dated informed consent document must be maintained in the study files at the investigative site and be available for Sponsor or designee review.

Each informed consent will contain Investigator contact information with a telephone number the subject or the subject's authorized representative can call 24 hours a day if they have medical concerns.

## **17. DATA HANDLING AND RECORDKEEPING**

### **17.1. Inspection of Records**

The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data and documents (such as tests performed as a requirement for participation in the study and other medical records required to confirm information contained in the case report form such as medical history) to the monitor.

Electronic case report forms will be used to collect subject data during the course of the trial. Electronic case report forms must be fully completed for each subject and signed by the Investigator upon completion. The Investigator or designated individual shall be responsible for recording trial data on the eCRFs. Access to the eCRFs will be by means of a unique username and password through a secure web-browser. Changes to the original data entries will trigger a reason for change dialogue box while the time, date and user making the change are automatically logged.

The Investigator is required to sign the eCRF on the appropriate page(s) to verify that he/she has reviewed the recorded data. Completed eCRFs will be verified by the Sponsor study monitors or designees at regular intervals during the trial. The Investigator will allow the monitor and other external regulatory body to review and inspect the study files, the eCRFs, subject medical records and other trial related documents as required.

### **17.2. Retention of Records**

The study center will retain all records related to the study in accordance with local and ICH GCP guidelines. Final signed eCRFs will be provided to the site at the end of the study for record retention.

## **18. PUBLICATION POLICY**

The institution and Investigators participating in this trial shall have no right to publish or present the results of this study without the prior written consent of the Sponsor.



## 19. LIST OF REFERENCES

1. DEWS Report. *The definition and classification of dry eye disease.*; 2007:75-92. Available at: <http://www.sciencedirect.com/science/article/pii/S1542012412700812>. Accessed April 29, 2014.
2. Paulsen, AJ, Cruickshanks, KJ, Fischer, ME, et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol.* 2014;*157*(4):799-806. doi:10.1016/j.ajo.2013.12.023.
3. Pflugfelder, SC. Antiinflammatory therapy for dry eye. *Am J Ophthalmol.* 2004;*137*(2):337-342. doi:10.1016/j.ajo.2003.10.036.
4. Xiidra® [package insert]. Lexington, MA: Shire Pharmaceuticals Inc; 2016.
5. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. *CLAO J Off Publ Contact Lens Assoc Ophthalmol Inc.* 1995;*21*(4):221-232.
6. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea.* 2003;*22*(7):640-650.

## **20. APPENDICES**

## APPENDIX 1: SUMMARY OF EVENTS

Procedures	Stage 1	Stage 2		
	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	Randomization		End of Study Visit
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (+2 days)
ICF, HIPAA and Significant Medical History	X			
Subject-rated assessment of ocular discomfort	X			
Subject-rated assessment of ocular discomfort		X <sup>c</sup>	X <sup>c</sup>	X <sup>c</sup>
Subject-rated assessment of eye dryness		X	X	X
Concomitant medication query	X	X	X	X
UPT <sup>a</sup>	X			X
Inclusion/Exclusion	X	X		
AE Assessment	X	X	X	X
assessment of bulbar conjunctival hyperemia	X	X		X
		X		X
BCVA	X	X		X
Slit lamp biomicroscopy	X	X		X
Corneal fluorescein staining	X	X		X
Unanesthetized Schirmer Test Assessment	X			
IOP measurement	X	X		X
Dilated ophthalmoscopy	X			X
Investigational product administration in-clinic	X <sup>b</sup>	X		
Dispense investigational product	X <sup>b</sup>	X		
	X <sup>b</sup>	X	X	
Collect investigational product		X <sup>b</sup>		X
		X	X	X

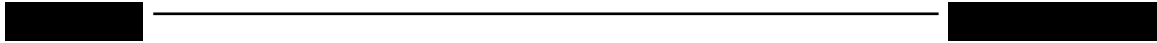
<sup>a</sup>Women of childbearing potential only; <sup>b</sup>Stage 1 Product

**APPENDIX 2: SUBJECT-RATED ASSESSMENT OF EYE DRYNESS**

Subjects will be asked to subjectively rate their eye dryness at Visits 2-4. Subjects will be instructed to rate eye dryness using the scales shown below and entered on a source document. The total length of the line from [REDACTED] to [REDACTED] is 100 mm. The length of the line between the [REDACTED] starting point and the first point where the subject's mark crosses the line will be measured and recorded in millimeters. This assessment is a general assessment of both eyes. There will not be a question for each individual eye.

**Instantaneous Evaluation of Eye Dryness**

Please place a single line across the line below to indicate the severity of your eye dryness [REDACTED]  
[REDACTED]:



**APPENDIX 3: SUBJECT-RATED ASSESSMENT OF OCULAR DISCOMFORT<sup>4</sup>**

Subjects will be asked to subjectively rate their ocular discomfort severity and frequency during the course of this study. [REDACTED]

[REDACTED] This assessment will be collected at Visit 1 (Screening) for eligibility. Further, subjects will be instructed to rate their discomfort [REDACTED] using the scales shown below [REDACTED]. The total length of the lines from [REDACTED] to [REDACTED] and [REDACTED] to [REDACTED] are 100 mm. The length of the line between the [REDACTED] on the severity scale or [REDACTED] on the frequency scale starting point and the first point where the subject's mark crosses the line will be measured and recorded in millimeters. This assessment is a general assessment of both eyes. There will not be a question for each individual eye.

**OCULAR DISCOMFORT SEVERITY ASSESSMENT**

Please place a single line across the line below to indicate how severe, [REDACTED] you feel your eye discomfort (for example, dryness or irritation) was:

[REDACTED] \_\_\_\_\_ [REDACTED]

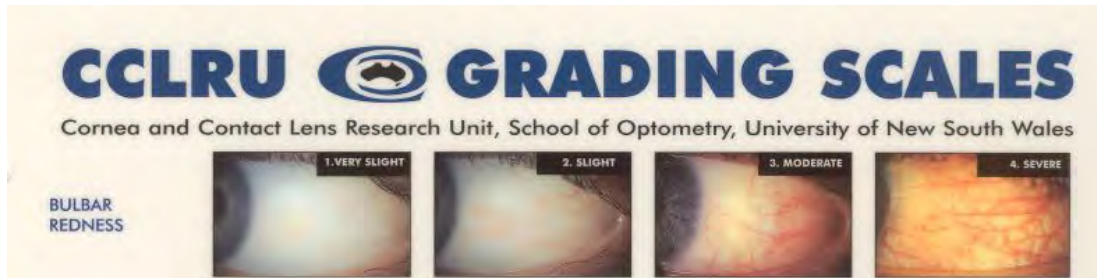
**OCULAR DISCOMFORT FREQUENCY ASSESSMENT**

Please place a single line across the line below to indicate how often, [REDACTED] you feel your eye discomfort (for example, dryness or irritation) was:

[REDACTED] \_\_\_\_\_ [REDACTED]

**APPENDIX 4: [REDACTED] ASSESSMENT OF BULBAR CONJUNCTIVAL HYPEREMIA**

[REDACTED] bulbar conjunctival hyperemia at Visits 1, 2, and 4 using the CCLRU Grading Scale.



- (0) None
- (1) Very Slight
- (2) Slight
- (3) Moderate
- (4) Severe

**APPENDIX 5: UNANESTHETIZED SCHIRMER TEST EVALUATION**

Unanesthetized Schirmer Test evaluation will be conducted at Visit 1 (Screening). Identical Schirmer Test strips will be supplied to each site. When conducting assessments room temperature and humidity should be relatively consistent throughout each visit and throughout the study. Please make certain to allow at least 20 minutes between any corneal staining evaluations and the unanesthetized Schirmer Test.

**Unanesthetized Schirmer Test**

- While still in the plastic sheath, fold the rounded end of the unanesthetized Schirmer Test strip at the first line on the strip (closest to the rounded end). Additionally, fold a partial second fold at the halfway point of the strip so that the strip does not lie directly in the subject's line of sight.
- Remove the right eye strip from the sheath.
- Ask the subject to look up and gently draw the right lower lid in a downward and temporal direction.
- Place the rounded end of the strip toward the temporal one-third of the lower eyelid.
- Repeat this procedure in the left eye.
- Darken the room, but ensure that the Large E or the ETDRS chart is visible.
- Instruct the subject to relax and look at the chart while blinking normally or have subject gently close eyes.
- Strips are removed after 5 minutes.
- After removing the strips, with a pen draw a horizontal line across the leading edge of moisture and a second horizontal line across the lowest point of moisture.
- Using a ruler and/or the millimeters recorded on the strips, measure a point halfway between the 2 lines and record this as the amount of wetting.
- Retain Schirmer strips in source documentation.

**APPENDIX 6: BEST-CORRECTED VISUAL ACUITY**

BCVA will be conducted at Visits 1, 2, and 4.

Visual acuity testing should precede any examination requiring contact with the eye or instillation of study dyes. LogMAR visual acuity must be assessed using an ETDRS or modified ETDRS chart. Visual acuity testing should be performed with best correction using subject's own corrective lenses (spectacles only) or pinhole refraction.

An ETDRS or modified ETDRS chart may be used. If a Lighthouse chart is used (24.5" by 25"; either reflectance or retro-illuminated), the subject must view the chart from a distance of exactly 4 meters (13.1 feet). If smaller reproductions (18" by 18", e.g., Prevent Blindness) are used, the subject viewing distance should be exactly 10 feet. Reflectance wall charts should be frontally illuminated (60-watt bulb or a well-lit room).

The subject should be positioned according to the elevation of the chart (either seated or standing) so that the chart is at a comfortable viewing angle. The right eye should be tested first. The subject should attempt to read each letter, line-by-line, left to right, beginning with line 1 at the top of the chart. The subject should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter instead of the number. The subject should be asked to read slowly, about 1 letter per second, to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response. If the subject changes a response before he has read aloud the next letter, then the change must be accepted.

Maximum effort should be made to identify each letter on the chart encouraging the subject to guess. When it becomes evident that no further meaningful readings can be made, the examiner should stop the test. The number of letters missed or read incorrectly should be noted.

**In order to provide standardized and well-controlled assessments of visual acuity during the study, consistently use the same lighting conditions during the entire study.**

Calculations:  $\text{logMAR VA} = \text{Baseline value} + (n \times 0.02)$

where: the baseline value is the logMAR number of the last line read (at least 1 letter read correctly in this line), and

“n” is the total number of letters missed up to and including the last line read, and

“0.02” is the value for each letter



**APPENDIX 7: SLIT LAMP BIOMICROSCOPY**

The biomicroscopy exam will be performed at Visits 1, 2, and 4. It should be performed with the slit lamp using a beam of width and intensity to provide optimal evaluation of anterior segment.

This procedure will be performed in the same manner for all subjects observed at the Investigator's site.

**Lashes**

0 = Normal

1 = Abnormal

**Eyelid****Eyelid Margin Hyperemia (lower eyelid):**

0 =	Normal	Normal age-appropriate redness and vasculature.
1 =	Mild	Slightly dilated blood vessels; vessels colored pink; present in greater than 25% of the lower eyelid margin
2 =	Moderate	More apparent dilation of blood vessels; vessel color red, present in greater than 25% of the lower eyelid margin.
3 =	Severe	Increased vascularity of the eyelid margin, numerous and obvious dilated blood vessels, deep red in color, present in greater than 25% of the lower eyelid margin.
4 =	Very Severe	Clearly increased vascularity of the eyelid margin; numerous dilated blood vessels deep red color, present in greater than 75% of the lower eyelid margin.

**Character of Meibomian Gland Content (middle part of lower lid, n = 10)**

0 =	Normal	Clear liquid
1 =	Mild	Hazy, turbid liquid
2 =	Moderate	Turbid liquid with clumps
3 =	Severe	Solid (paste)

**The most severe finding in any one meibomian gland should be recorded for this evaluation****Expressibility of Meibomian Gland (middle part of lower lid, n = 10)**

0 =	Normal	9 – 10 glands expressible
1 =	Mild	6 – 8 glands expressible
2 =	Moderate	3 – 5 glands expressible
3 =	Severe	1 – 2 glands expressible

**Edema**

0 = Normal, no swelling of the lid tissue

1 = Abnormal

**Conjunctiva****Edema**

0 = Normal, no swelling of the conjunctiva

1 = Abnormal

## **Cornea**

### Infiltrates

0 = Absent

1 = Present

### Endothelial Changes

0 = Normal, None

1 = Abnormal, pigment, keratoprecipitates, guttata

### Edema

0 = Normal None, transparent and clear

1 = Abnormal

## **Anterior Chamber**

### Cells

0 = Normal, No cells seen

1 = Abnormal (+ to +++ cells)

### Flare

0 = Normal, No Tyndall effect

1 = Abnormal, Tyndall beam in the anterior chamber

## **Lens Pathology**

0 = Normal; no opacity in the lens

1 = Abnormal; existing opacity in the lens; aphakic or pseudophakic eyes or other abnormal findings.

**Sclera**

Injection

0 = Normal, without any redness

1 = Abnormal

**APPENDIX 8: CORNEAL FLUORESCEIN STAINING**

Corneal staining will be performed at Visit 1, 2, and 4. Corneal staining assessment will be performed for both eyes using methods developed by the NEI Dry Eye Workshop<sup>5,6</sup> with separate strips used for each eye.

**Evaluation Technique**

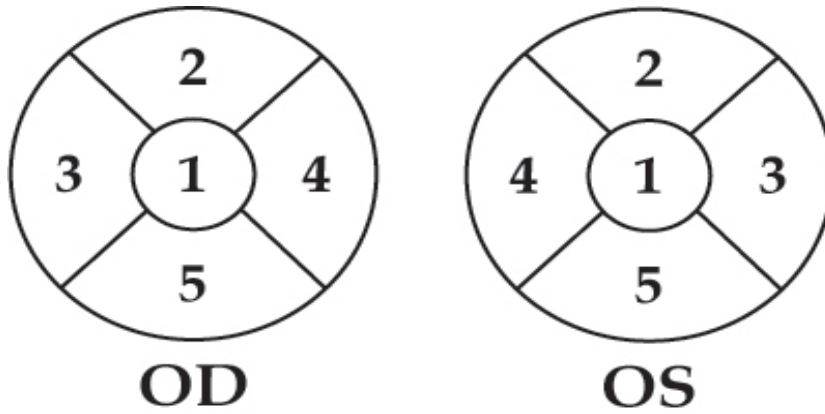
1. Use a Wratten #12 barrier filter in the assessment of fluorescein staining to enhance the appearance of the fluorescein.
2. Use sufficient unpreserved saline solution (study stock) to wet the entire area of fluorescein impregnation on a 1.0 mg strip. If the strip becomes too saturated, please discard and begin again with a new strip.
3. Within 15 seconds of wetting the strip, taking care not to touch the strip to the eye, instill the fluorescein sodium on the inferior palpebral conjunctiva.
4. Instruct the subject to blink several times to distribute the fluorescein staining.
5. Examine the cornea 2 minutes after instillation of fluorescein
6. Use a cobalt blue illumination (465 nm to 490 nm) and a 3-mm-wide scanning beam in each eye.
7. Compare corneal fluorescein staining in each eye with the standard by scoring each of the 5 corneal sections as described below:

**Scoring system**

1. Grade each of 5 sections of cornea (superior, inferior, nasal, temporal, central)
2. Provide grades for each of the 5 sections:
  - a. Grade by NEI scale (definition below) as 0, 1 (mild), 2 (moderate), 3 (severe)
3. Total score is obtained by summing each of the 5 sections of the cornea
  - a. NEI score will be from 0-15
4. Definitions
  - a. NEI Scoring System (0, 1, 2, 3)
    - i. Grade 0  
No visible staining within the section of cornea being evaluated
    - ii. Grade 1 MILD  
Small amount of micropunctate staining within the section of cornea being evaluated
    - iii. Grade 2 MODERATE  
Medium amount of micropunctate staining within the section of cornea being evaluated or mild amount of macropunctate stain

## iv. Grade 3 SEVERE

Significant amount of micropunctate or macropunctate staining within the section of cornea being evaluated



 Grade 0

 Grade 2

 Grade 1

 Grade 3

**APPENDIX 9: IOP MEASUREMENT**

IOP measurements will be performed utilizing Goldmann applanation tonometry according to the Investigator's standard procedure. All pressure will be recorded in mmHg. IOP assessments will occur at study Visits 1, 2, and 4.

**APPENDIX 10: DILATED OPHTHALMOSCOPY**

Dilated ophthalmoscopy will include assessment of the optic nerve head for pallor and cupping (cup to disc ratio) and will be performed at Visit 1 (Screening) and Visit 4 after the administration of all other study assessments (except for symptom assessments). After the ophthalmoscopy procedure, the Investigator will determine if findings are within normal limits or are abnormal. For abnormal findings at Visit 1 (Screening), the Investigator will determine whether or not the abnormality would exclude subject from study participation.





