NCT02188160

Study ID:
KPI-121-C-002

Study Title:
A Phase 2, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease

Date:
26 Sep 2014

**KALA PHARMACEUTICALS, INC.**
**Clinical Protocol KPI-121-C-002**

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| **Project:** | KPI-121 |
| **Compound Number/Name:** | KPI-121 |
| **Protocol Number:** | KPI-121-C-002 |
| **Protocol Title:** | A Phase 2, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease |
| **Sponsor:** | Kala Pharmaceuticals, Inc.<br>100 Beaver St., Suite 201<br>Waltham, MA 02453 |
| **Medical Monitor:** | [redacted] |
| **Issue Date:** | Original: 22 May 2014<br>Amendment 1: 10 Jun 2014<br>Amendment 2: 02 Jul 2014<br>Amendment 3: 21 Jul 2014<br>Amendment 4: 07 Aug 2014<br>Amendment 5: 12 Sep 2014<br>Amendment 6: 26 Sep 2014 |
| **Approved:** | 26 Sep 2014 |

[redacted]

**KALA PHARMACEUTICALS, INC.**
**Clinical Protocol KPI-121-C-002**
**Investigator Signature Page**

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| **Contact for Serious Adverse Events:** | [redacted] |

**Investigator Name (printed or typed):**

_____

**Investigator's Signature:**

_____ _____

## SYNOPSIS

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|---|---|
| Study Title: | KPI-121-C-002: A Phase 2, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease |
| Objectives: | 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. |
| Study Population: | The study population will consist of subjects diagnosed with dry eye disease. |
| Number of Subjects | Up to 400 subjects who are diagnosed with dry eye disease will be screened. Among those screened, approximately 150 subjects will be randomized to KPI-121 0.25% ophthalmic suspension or vehicle. |
| Investigational Products: | KPI-121 0.25% ophthalmic suspension and vehicle will be supplied as investigational product. |
| Route and Duration of Administration: | 1 to 2 drops of investigational product will be instilled in each eye four times per day (QID) for up to 28 days. |
| Study Design: | This is a Phase 2, 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.<br><br>Approximately 400 subjects will be screened and up to 150 subjects will be randomized at up to 12 centers located in the United States (US).<br><br>Subjects will be randomized to 1 of 2 study arms in an approximate 1:1 ratio. The study arms are: 1) KPI-121 0.25% ophthalmic suspension administered as 1-2 drops in each eye QID for up to 28 days or 2) vehicle administered as 1-2 drops in each eye QID for up to 28 days.<br><br>Furthermore, subjects will be assigned to a study arm based on the stratification of:<br>• Subject's day prior to Visit 2 (Day 1) [redacted] score |

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| | [redacted] AND<br>• Study eye baseline investigator-rated bulbar conjunctival hyperemia score [redacted]<br><br>This study will include up to 6 clinic visits over 6 weeks. At Visit 1 Screening (14 ± 1 days prior to Day 1), subjects who meet screening inclusion/exclusion criteria will begin a 2-week run-in period during which they will be treated with 1-2 drops of single-masked vehicle in each eye QID for 14 ± 1 days.<br><br>At Visit 2, Randomization (Day 1), subjects who continue to meet inclusion/exclusion criteria will be eligible for randomization to 1 of the 2 arms of the study (i.e., KPI-121 0.25% ophthalmic suspension or vehicle). Following randomization, subjects will be instructed to return to the clinic to have a complete study evaluation at Study Visits 4 and 6 (Days 15 ± 1 day and 29 ± 1 day, respectively). Subjects will further be instructed to return to the clinic for diary collection and in-clinic symptom assessment only at Visits 3 and 5 (Days 8 ± 1 day and 22 ± 1 day, respectively). The last dose of investigational product and the final study visit will occur upon completion of 28 ± 1 days of exposure to investigational product. Subjects will be released from the study at the end of Visit 6 (Day 29 ± 1 day).<br><br>Assessments in this study will include:<br>• Subject-rated assessment of ocular discomfort [redacted]<br>• [redacted]<br>• Investigator-rated assessment of bulbar conjunctival hyperemia<br>• [redacted]<br>• Best corrected visual acuity (BCVA)<br>• Slit lamp biomicroscopy<br>• Corneal fluorescein staining<br>• Unanesthetized Schirmer Test evaluation<br>• Lissamine Green conjunctival staining<br>• Intraocular pressure (IOP) measurement |

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| | • Dilated ophthalmoscopy |
| Efficacy Endpoints | **Primary Efficacy Endpoints:**<br><br>Comparison of mean bulbar conjunctival hyperemia [redacted] between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 6<br><br>Comparison of mean [redacted] Severity Assessment Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 5 through the day before Visit 6<br><br>**Secondary Efficacy Endpoints:**<br><br>Comparison of mean corneal fluorescein staining between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 4<br>• Visit 6<br><br>Comparison of mean bulbar conjunctival hyperemia [redacted] between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 4<br><br>Comparison of mean [redacted] Severity Assessment Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 3 through the day before Visit 4<br><br>**Exploratory Efficacy Endpoints**<br><br>Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for bulbar conjunctival hyperemia [redacted]<br>• Visit 4 as compared to Visit 2<br>• Visit 6 as compared to Visit 2 |

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| | [redacted]<br><br>[redacted]<br><br>Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for [redacted] Severity Assessment Scores:<br>• Visit 3 through the day before Visit 4 as compared to Days -7 to -1<br>• Visit 5 through the day before Visit 6 as compared to Days -7 to -1.<br><br>Comparison of mean [redacted] Frequency Assessment Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 3 through the day before Visit 4<br>• Visit 5 through the day before Visit 6<br><br>Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for [redacted] Frequency Assessment Scores:<br>• Visit 3 through the day before Visit 4 as compared to Days -7 to -1<br>• Visit 5 through the day before Visit 6 as compared to Days -7 to -1.<br><br>Comparison of mean Subject-Rated Ocular Discomfort Severity Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 4<br>• Visit 6 |

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| | Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for Subject-Rated Ocular Discomfort Severity Scores:<br>• Visit 4 as compared to Visit 2<br>• Visit 6 as compared to Visit 2<br><br>Comparison of mean Subject-Rated Ocular Discomfort Frequency Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 4<br>• Visit 6<br><br>Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for Subject-Rated Ocular Discomfort Frequency Scores:<br>• Visit 4 as compared to Visit 2<br>• Visit 6 as compared to Visit 2<br><br>Comparison of mean difference within KPI-121 0.25% ophthalmic suspension group and within the vehicle group for corneal fluorescein staining:<br>• Visit 4 as compared to Visit 2<br>• Visit 6 as compared to Visit 2<br><br>Comparison of mean Lissamine Green conjunctival staining between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:<br>• Visit 4<br>• Visit 6<br><br>Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for Lissamine Green conjunctival staining:<br>• Visit 4 as compared to Visit 2<br>• Visit 6 as compared to Visit 2 |
| Safety Endpoints | • Assessment of adverse events (AEs)<br>• Slit lamp biomicroscopy<br>• IOP measurement<br>• BCVA |

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| | • Dilated Ophthalmoscopy |
| Eligibility Criteria: | **Inclusion Criteria:**<br><br>At Visit 1 (Screening) and Visit 2 (Randomization), individuals of either gender or any race will be eligible for study participation if they:<br>1. Provide written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to any study-related procedures.<br>2. Are 18 years of age or older.<br>3. Are willing and able to follow instructions and can be present for the required study visits for the duration of the study, including:<br>a. Single-masked investigational product use compliance of at least 80% during the final week of the run-in phase AND<br>b. [redacted]<br>4. Have a documented clinical diagnosis of dry eye disease in both eyes.<br>5. Have ongoing dry eye disease as defined by the following criteria in the same eye or both eyes:<br>a. A corneal fluorescein staining score at **Visit 1 and Visit 2** of [redacted] [National Eye Institute (NEI) scale] AND<br>b. Bulbar conjunctival hyperemia **at Visit 1 and Visit 2** of [redacted] as assessed using the Cornea and Contact Lens Research Unit (CCLRU) scale AND<br>c. A score of [redacted] Severity Assessment **at Visit 1 AND** a score of [redacted] Severity [redacted] **Visit 2 (Day 1)** AND<br>d. An unanesthetized Schirmer Test score **at Visit 1** of [redacted]<br>6. Have normal lid anatomy.<br>7. Are women of child bearing potential (WOCBP) who |

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| | are not pregnant or lactating and not sexually active (i.e., abstinent) for 14 days prior to Visit 1 and willing to remain so through 30 days following Visit 6 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:<br>a. Intrauterine device (IUD) in place for at least **3 months** prior to Visit 1 and continuing through Visit 6 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.<br>b. Barrier method (condom or diaphragm) with spermicide for at least **3 months** prior to Visit 1 and continuing through Visit 6 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.<br>c. Stable hormonal contraceptive for at least **3 months** prior to Visit 1 and continuing through Visit 6 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.<br>**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.<br>d. In a monogamous relationship with a |

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| | surgically sterilized (i.e., vasectomized) partner at least **6 months** prior to Visit 1 through Visit 6 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.<br>8. Are postmenopausal women (i.e., no menstrual cycle for at least one year prior to Visit 1) or are women who have undergone 1 of the following sterilization procedures at least 6 months prior to Visit 1:<br>a. Bilateral tubal ligation<br>b. Hysterectomy<br>c. Hysterectomy with unilateral or bilateral oophorectomy.<br>d. Bilateral oophorectomy<br><br>**Exclusion Criteria:**<br><br>In order for subjects to be eligible at Visit 1 (Screening) and Visit 2 (Randomization) they may not:<br>1. Have a known hypersensitivity or contraindication to the investigational product(s) or their components.<br>2. Have used any of the following medications within **30 days** prior to Screening (Visit 1) or for the duration of the study:<br>a. Ocular, inhaled, or intranasal corticosteroids<br>b. Ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of ≤ 81 mg/day of acetylsalicylic acid (ASA or aspirin)<br>c. Topical ocular antibiotics<br>d. Topical ocular antihistamines or mast cell stabilizers<br>e. Oral antihistamines<br>f. Topical or nasal vasoconstrictors<br>3. Have used any of the following medications within **60 day**s prior to Screening (Visit 1) or for the duration of the study: |

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| | a. Topical cyclosporine (Restasis®)<br>b. Any form of topical loteprednol etabonate (LE)<br>4. Have altered oral dosing of the following within **30 days** prior to Screening (Visit 1) or anticipate alteration of dosing during the study:<br>a. tetracycline compounds (e.g., tetracycline, doxycycline, or minocycline)<br>b. Omega-3 or Omega-6 supplements<br>5. Have altered dosing of the following medications within **6 months** prior to Screening (Visit 1) or anticipate alteration of dosing during the study:<br>a. Anticholinergics<br>b. Antidepressants<br>c. Isotretinoin<br>d. Oral corticosteroids<br>e. Systemic immunosuppressive agents<br>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:<br>a. Eyelash growth medications<br>b. Eye drops, gels, or artificial tears<br>7. Be unwilling to abstain from the use TNF-blocking agents (e.g. etanercept, adalimumab, infliximab) **at Visit 1 (Screening)** and for the duration of the study.<br>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 (Randomization)**.<br>9. Be unwilling to abstain from wearing contact lenses for **14 days** prior to Visit 1 (Screening) and for the duration of the study.<br>10. Be monocular or have a BCVA, using corrective lenses if necessary, of +1.0 logMAR or worse as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS).<br>11. Have had penetrating intraocular surgery within **3 months** prior to Visit 1 (Screening) or anticipate |

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| | requiring penetrating intraocular surgery during the study.<br>12. Have had eyelid surgery within **6 months** prior to Visit 1 (Screening) or anticipate requiring eyelid surgery during the study.<br>13. Have congenitally absent lacrimal glands or meibomian glands.<br>14. Have had selective laser trabeculoplasty (SLT) within **3 months** prior to Visit 1 (Screening) or anticipate requiring SLT.<br>15. 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.<br>**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.<br>16. Have had corneal refractive surgery, glaucoma surgery, or corneal transplantation (full thickness, anterior or posterior) within **1 year** prior to Visit 1 (Screening)<br>**NOTE:** This exclusion also applies if surgery was performed greater than 1 year prior to Visit 1 but the Investigator considers the subject to be unstable and/or require medication.<br>17. Have a diagnosis of:<br>a. Ongoing ocular infection<br>b. Moderate to severe pinguecula or pterygia<br>c. Stevens-Johnson Syndrome<br>d. Significant conjunctival scarring<br>e. Significant anterior blepharitis<br>f. Severe/serious ocular condition that in the judgment of the investigator could confound study assessments or limit compliance.<br>g. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance.<br>18. Have Corneal Fluorescein Staining with diffuse |

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| | confluent staining more than 33% of area (focal confluent staining is acceptable), over 5 filaments or epithelial defects.Have active or have had an outbreak of herpetic keratitis within **1 year** of Visit 1.<br>19. [redacted]<br>20. 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.<br>21. Have been exposed to an investigational drug within **30 days** prior to Visit 1.<br>22. Be an employee of the site that is directly involved in the management, administration, or support of this study or be an immediate family member of the same.<br>23. Have a documented history of alcohol and/or drug abuse.<br>24. 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. |

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| AR | Adverse Reaction |
| AE | Adverse Event |
| BCVA | Best Corrected Visual Acuity |
| BL | Baseline |
| °C | Degrees Celsius |
| CCLRU | Cornea and Contact Lens Research Unit |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| eCRF | Electronic Case Report Form |
| EE | Efficacy Evaluable |
| 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 |
| KCS | Keratoconjunctivitis sicca |
| KPI | Kala Pharmaceuticals, Inc. |
| L | Liter |
| 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 |
| NSAID | Non-steroidal anti-inflammatory drug |
| PDF | Portable Document Format |
| QID | Four Times Daily |
| SAE | Serious Adverse Event |
| [redacted] | [redacted] |

| | |
|---|---|
| SAR | Suspected Adverse Reaction |
| SLT | Selected Laser Trabeculoplasty |
| 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 |

# 1. INTRODUCTION

Over 7 million people in the United States experience dry eye symptoms of some severity (DEWS Report, 2007). 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. Patients with dry eye disease may experience significant ocular discomfort and reduced visual function, thus resulting in a decreased quality of life or work productivity[1].

Current treatment of dry eye disease generally begins with artificial tear replacement and then expands to include topical anti-inflammatory therapy and punctal occlusion[1]. Topical cyclosporine (Restasis®) is currently the only Food and Drug Administration (FDA) approved prescription medication for use in patients with dry eye disease. Restasis® is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS, but a significant percentage of patients experience adverse reactions to the drug, including ocular irritation upon instillation, slow onset of response, and limited efficacy.

Inflammation has a prominent role in the development and proliferation of dry eye disease[2]. Factors adversely affecting tear film stability and osmolarity can initiate an inflammatory cascade that leads to the development of a self-perpetuating inflammatory cycle[2]. 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[3].

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®; 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. Study KPI-121-C-002 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.

## 1.1. DESCRIPTION OF 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. Kala is developing this improved LE formulation for the treatment of dry eye disease.

KPI-121 0.25% ophthalmic suspension contains 0.25% (w/v) LE in an isotonic formulation that is buffered to maintain pH 5.0 – 7.0. It is a sterile, aqueous submicron suspension of LE and is filled in a white, low-density polyethylene plastic dropper bottle with a white, controlled-drop polyethylene tip and a polypropylene cap. Each bottle contains 5.5 mL nominal fill volume.

The vehicle control has the same composition as KPI-121 0.25% ophthalmic suspension but does not contain LE. The vehicle is essentially isotonic and is buffered to maintain pH 5.0 – 7.0. It is a sterile, aqueous solution supplied in the same white, low-density polyethylene plastic dropper bottle with the same white, controlled-drop polyethylene tip and white polypropylene closure as KPI-121 0.25% ophthalmic suspension.

## 1.2. JUSTIFICATION FOR ROUTE OF ADMINISTRATION AND DOSE SELECTION

KPI-121 will be administered as a topical ophthalmic suspension. Subjects are expected to self-administer 1 to 2 drops of either KPI-121 0.25% ophthalmic suspension or vehicle QID.

Direct instillation is the most efficient method for delivery to the ocular surface and is an accepted and widely used method for topical application to the eye. This study will examine safety and efficacy of KPI-121 0.25% ophthalmic suspension versus vehicle dosed QID for 28 days in subjects with dry eye disease.

For additional details on the toxicology studies and the respective safety multiples, see the Investigator's Brochure.

## 1.3. GCP COMPLIANCE

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization (ICH) guidelines, Good Clinical Practices (GCP) guidelines and other applicable regulatory requirements.

## 1.4. POPULATION TO BE STUDIED

Up to 400 subjects who are diagnosed with dry eye disease will be screened for this study. Approximately 150 subjects of these subjects will be randomized to either KPI-121 0.25% ophthalmic suspension or vehicle.

# 2. TRIAL OBJECTIVES AND PURPOSE

## 2.1. 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.

# 3. TRIAL DESIGN

## 3.1. PRIMARY EFFICACY ENDPOINTS

Comparison of mean bulbar conjunctival hyperemia [redacted] between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 6

Comparison of mean [redacted] Severity Assessment Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 5 through the day before Visit 6

## 3.2. SECONDARY EFFICACY ENDPOINTS

Comparison of mean corneal fluorescein staining between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

Comparison of mean bulbar conjunctival hyperemia [redacted] between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4

Comparison of mean [redacted] Severity Assessment Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 3 through the day before Visit 4

## 3.3. EXPLORATORY EFFICACY ENDPOINTS

Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for bulbar conjunctival hyperemia [redacted]

- Visit 4 as compared to Visit 2
- Visit 6 as compared to Visit 2

[redacted]

[redacted]

Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for [redacted] Severity Assessment Scores:

- Visit 3 through the day before Visit 4 as compared to Days -7 to -1
- Visit 5 through the day before Visit 6 as compared to Days -7 to -1.

Comparison of mean [redacted] Frequency Assessment Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 3 through the day before Visit 4
- Visit 5 through the day before Visit 6

Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for [redacted] Frequency Assessment Scores:

- Visit 3 through the day before Visit 4 as compared to Days -7 to -1
- Visit 5 through the day before Visit 6 as compared to Days -7 to -1.

Comparison of mean Subject-Rated Ocular Discomfort Severity Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for Subject-Rated Ocular Discomfort Severity Scores:

- Visit 4 as compared to Visit 2
- Visit 6 as compared to Visit 2

Comparison of mean Subject-Rated Ocular Discomfort Frequency Scores between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for Subject-Rated Ocular Discomfort Frequency Scores:

- Visit 4 as compared to Visit 2
- Visit 6 as compared to Visit 2

Comparison of mean difference within KPI-121 0.25% ophthalmic suspension group and within the vehicle group for corneal fluorescein staining:

- Visit 4 as compared to Visit 2
- Visit 6 as compared to Visit 2

Comparison of mean Lissamine Green conjunctival staining between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

Comparison of mean difference within the KPI-121 0.25% ophthalmic suspension group and within the vehicle group for Lissamine Green conjunctival staining:

- Visit 4 as compared to Visit 2
- Visit 6 as compared to Visit 2

**Table 1: SUMMARY OF EFFICACY ENDPOINTS**
**(All comparisons will be between the KPI-121 0.25% ophthalmic suspension and vehicle groups)**

| Evaluation | Comparison | Visit | 1° | 2° | Exploratory |
|---|---|---|---|---|---|
| [redacted] Bulbar Conjunctival Hyperemia | Mean values | 6 | X | | |
| [redacted] Bulbar Conjunctival Hyperemia | Mean values | 4 | | X | |
| [redacted] Bulbar Conjunctival Hyperemia | Mean change from baseline (BL) | 4 vs. 2 | | | X |
| [redacted] Bulbar Conjunctival Hyperemia | Mean change from BL | 6 vs. 2 | | | X |
| [redacted] | [redacted] | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] |
| [redacted] | [redacted] | [redacted] | | | [redacted] |
| [redacted] Severity | Mean values | 5 through day before 6 | X | | |
| [redacted] Severity | Mean values | 3 through day before 4 | | X | |
| [redacted] Severity | Mean change from BL | 3 through day before 4 vs. Day -7 through Day -1 | | | X |
| [redacted] Severity | Mean change from BL | 5 through day before 6 vs. Day -7 through Day -1 | | | X |
| [redacted] Frequency | Mean values | 3 through day before 4 | | | X |

| Evaluation | Comparison | Visit | 1° | 2° | Exploratory |
|---|---|---|---|---|---|
| [redacted] Frequency | Mean values | 5 through day before 6 | | | X |
| [redacted] Frequency | Mean change from BL | 3 through day before 4 vs. Day -7 through Day -1 | | | X |
| [redacted] Frequency | Mean change from BL | 5 through day before 6 vs. Day -7 through Day -1 | | | X |
| Corneal Fluorescein Staining | Mean values | 4 | | X | |
| Corneal Fluorescein Staining | Mean values | 6 | | X | |
| Corneal Fluorescein Staining | Mean change from BL | 4 vs. 2 | | | X |
| Corneal Fluorescein Staining | Mean change from BL | 6 vs. 2 | | | X |
| Lissamine Green Staining | Mean values | 4 | | | X |
| Lissamine Green Staining | Mean values | 6 | | | X |
| Lissamine Green Staining | Mean change from BL | 4 vs. 2 | | | X |
| Lissamine Green Staining | Mean change from BL | 6 vs. 2 | | | X |
| Subject-Rated Ocular Discomfort Severity Scores | Mean values | 4 | | | X |
| Subject-Rated Ocular Discomfort Severity Scores | Mean values | 6 | | | X |
| Subject-Rated Ocular Discomfort Severity Scores | Mean change from BL | 4 vs. 2 | | | X |
| Subject-Rated Ocular Discomfort Severity Scores | Mean change from BL | 6 vs. 2 | | | X |

| Evaluation | Comparison | Visit | 1° | 2° | Exploratory |
|---|---|---|---|---|---|
| Subject-Rated Ocular Discomfort Frequency Scores | Mean values | 4 | | | X |
| Subject-Rated Ocular Discomfort Frequency Scores | Mean values | 6 | | | X |
| Subject-Rated Ocular Discomfort Frequency Scores | Mean change from BL | 4 vs. 2 | | | X |
| Subject-Rated Ocular Discomfort Frequency Scores | Mean change from BL | 6 vs. 2 | | | X |

## 3.4. SAFETY ENDPOINTS

- Assessment of AEs
- Slit lamp biomicroscopy
- IOP measurement
- BCVA
- Dilated Ophthalmoscopy

## 3.5. DESCRIPTION OF TRIAL DESIGN

This is a Phase 2, 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 6 clinic visits, including 2 weeks of single-masked vehicle run-in followed by up to 28 days of investigational product dosing (KPI-121 0.25% ophthalmic suspension or vehicle).

Up to 400 subjects at up to 12 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 run-in period of QID dosing with single masked vehicle. At Visit 2 (Day 1/Randomization), approximately 150 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.

The study eye will be selected based on the study qualification criteria entered into the Interactive Web Response System (IWRS) for stratification at randomization. If both eyes qualify for the study with exactly the same values for ocular entry criteria, IWRS will choose the study eye as OD. 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 the following 2 stratification criteria:

- Subject's day prior to Visit 2 (Day 1) [redacted] score [redacted] AND
- Study eye baseline [redacted] bulbar conjunctival hyperemia score [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, and study staff will be masked during the randomization process and through the remainder of the study.

Subjects will return to the clinic for complete study evaluation at Visits 4 and 6 (Day 15 ± 1 day and Day 29 ± 1 day, respectively). Subject will also return at Visits 3 and 5 (Days 8 ± 1 day and 22 ± 1 day, respectively) to [redacted] assess concomitant medication use and adverse events. Subjects will discontinue dosing and be released from the study at Visit 6 (Day 29 ± 1 day).

A summary of events is provided in Appendix 1. Assessments in this study will include:

- Subject-rated ocular discomfort assessment (Appendix 2)
- [redacted] assessment (Appendix 3)
- Investigator-rated assessment of bulbar conjunctival hyperemia (Appendix 4)
- Unanesthetized Schirmer Test (Appendix 5)
- BCVA (Appendix 6)
- Slit lamp biomicroscopy (Appendix 7)
- Corneal fluorescein staining (Appendix 8)
- Lissamine Green conjunctival staining (Appendix 9)
- IOP measurement (Appendix 10)
- Dilated ophthalmoscopy (Appendix 11)
- [redacted] (Appendix 12)
- [redacted]
- Concomitant medication use assessment
- Assessments of AEs

A study schematic follows (Figure 1).

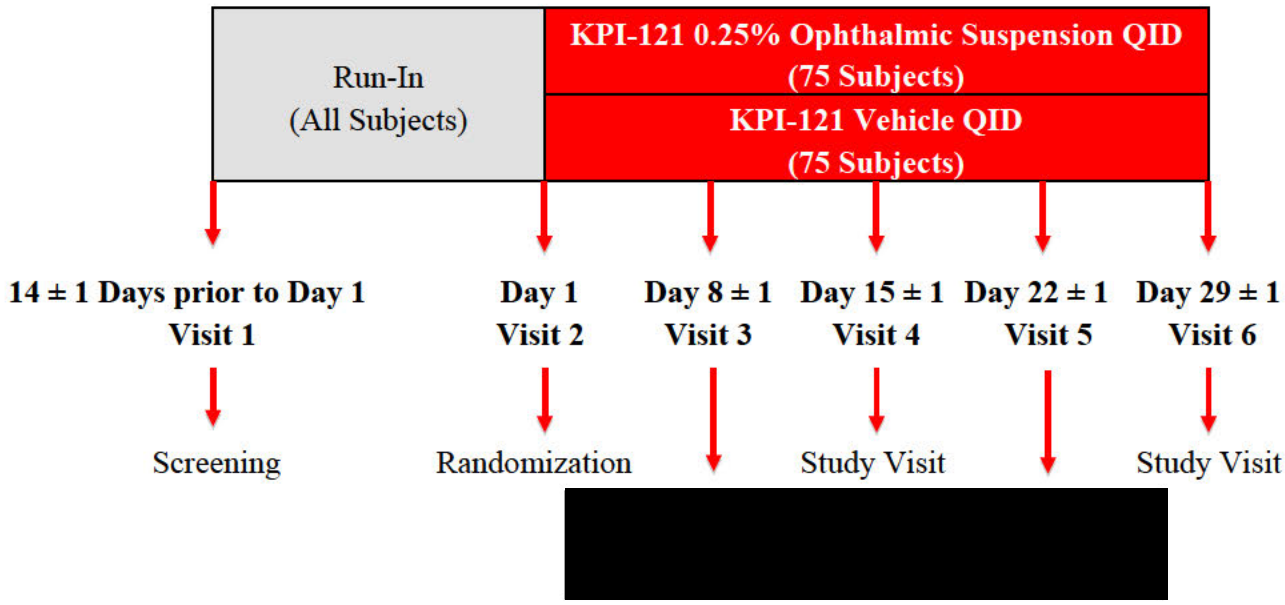



**FIGURE 1: STUDY SCHEMATIC**

### 3.5.1. Investigational product

KPI-121 0.25% w/v 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 7.5 mL, white, low-density polyethylene plastic bottle with a white, controlled-drop polyethylene tip and a white polypropylene cap. Each bottle contains 5.5 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.

Subject will be instructed to shake the investigational product bottle prior to each instillation.

**Table 2: COMPOSITION OF KPI-121 0.25% (W/V) DRUG PRODUCT**

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

**Table 3: COMPOSITION OF VEHICLE**

| Ingredient | Function | Concentration (% w/v) |
|---|---|---|
| [redacted] | [redacted] | [redacted] |

At Visit 1, eligible subjects will receive 2 bottles of single-masked, investigational product (vehicle) from a common site level supply. The bottle labels for the single-masked period contain the following information: sponsor name, protocol number, lot number, storage temperature, and required statement(s) per the appropriate regulatory agency.

The randomized, double-masked, investigational product kit consists of a box that contains 3 dropper bottles of investigational product. At Visit 2 (Day 1/Randomization), subjects will receive 2 bottles of double-masked investigational product (KPI-121 0.25% ophthalmic suspension or vehicle) from their assigned kit. At Visit 4 (Day 15 ± 1 day), subjects will receive 1 additional bottle of investigational product from their assigned kit. All bottles will

be returned to the site at Visit 6 (Day 29 ± 1 day). The box labels and the dropper bottle labels will contain the following information: sponsor name, protocol number, randomization number, storage temperature, and required statement(s) per the appropriate regulatory agency.

All investigational products will be stored in a secure area with limited access at controlled room temperature (15-25°C/59 -77°F). Subjects will be instructed to shake the investigational product bottle prior to administering each dose. 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 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 QID dosing.

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."

### 3.5.2. Methods to Minimize Bias

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 who will be responsible for dispensing investigational product to subjects and instructing subjects regarding dosing of the investigational product. 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.

# 4. SELECTION OF SUBJECTS

## 4.1. SUBJECT INCLUSION AND EXCLUSION CRITERIA

### 4.1.1. Inclusion Criteria

At Visit 1 (Screening) and Visit 2 (Randomization), 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 the run-in phase AND
    b. [redacted] scoring of at least 80% in the final week of the run-in phase.
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. A corneal fluorescein staining score at **Visit 1 and Visit 2** of [redacted] 6 NEI scale AND
    b. Bulbar conjunctival hyperemia **at Visit 1 and Visit 2** of [redacted] as assessed using the CCLRU scale AND
    c. A score of [redacted] Severity Assessment **at Visit 1 AND** a score of [redacted] Severity **on the day prior to Visit 2 (Day 1)** AND
    d. An unanesthetized Schirmer Test score **at Visit 1** of [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 and willing to remain so through 30 days following Visit 6 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 and continuing through Visit 6 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 and continuing through Visit 6 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 and continuing through Visit 6 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 through Visit 6 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) or are women who have undergone 1 of the following sterilization procedures at least 6 months prior to Visit 1:
    a. Bilateral tubal ligation
    b. Hysterectomy
    c. Hysterectomy with unilateral or bilateral oophorectomy.
    d. Bilateral oophorectomy

### 4.1.2. Exclusion Criteria

In order for subjects to be eligible at Visit 1 (Screening) and Visit 2 (Randomization) 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 within **30 days** prior to Screening (Visit 1) 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 ≤ 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

3. Have used any of the following medications within **60 day**s prior to Screening (Visit 1) or for the duration of the study:
    a. Topical cyclosporine (Restasis®)
    b. Any form of topical LE
4. Have altered oral dosing of the following within **30 days** prior to Screening (Visit 1) 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 Screening (Visit 1) or anticipate alteration of dosing during the study:
    a. Anticholinergics
    b. Antidepressants
    c. Isotretinoin
    d. Oral corticosteroids
    e. Systemic immunosuppressive agents
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
    b. Eye drops, gels, or artificial tears
7. Be unwilling to abstain from the use 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 (Randomization)**.
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, using corrective lenses if necessary, of +1.0 logMAR or worse as assessed by 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 eyelid surgery within **6 months** prior to Visit 1 (Screening) or anticipate requiring eyelid surgery during the study.
13. Have congenitally absent lacrimal glands or meibomian glands.
14. Have had SLT within **3 months** prior to Visit 1 (Screening) or anticipate requiring SLT .
15. 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.

16. Have had corneal refractive surgery, glaucoma surgery, or corneal transplantation (full thickness, anterior or posterior) within **1 year** prior to Visit 1 (Screening)
    **NOTE:** This exclusion also applies if surgery was performed greater than 1 year prior to Visit 1 but the Investigator considers the subject to be unstable and/or require medication.
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), over 5 filaments or epithelial defects.
19. Have active or have had an outbreak of herpetic keratitis within **1 year** of Visit 1.
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 drug within **30 days** prior to Visit 1.
23. Be an employee of the site that is directly 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.

# 5. PROCEDURES

Written Informed Consent and HIPAA authorization will be obtained from all subjects prior to any study procedures being performed.

## 5.1. VISIT DESCRIPTION

### 5.1.1. 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 3-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.

- Non-ocular and ocular medical history
- Concomitant medication usage and medications taken during the 6 months prior to screening
- Inclusion/exclusion criteria
- Urine pregnancy test (UPT) for women of childbearing potential
- Subject-rated assessment of ocular discomfort
- [redacted] assessment
- BCVA
- Investigator-rated assessment of bulbar conjunctival hyperemia
- Slit Lamp Biomicroscopy
- Corneal fluorescein staining
- Lissamine Green conjunctival 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
- [redacted]

The first dose of single-masked investigational product will be taken in the clinic under the supervision of study personnel. Prior to administration, subjects will be instructed regarding proper instillation of investigational product. 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.

**Instructions to subject:**

- Dose single-masked run-in investigational product as instructed
- [redacted]
- [redacted]
- Return for Visit 2 scheduled in 14 ± 1 days.

### 5.1.2. Visit 2: Day 1 (Randomization)

The randomization visit will occur 14 ± 1 days after Visit 1 (Screening). This visit 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 4) will continue in the study. The following will be performed/assessed:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- [redacted]
- Used and unused single-masked run-in investigational product collected, counted, and compliance assessed (via subject diary)
- Subject-rated assessment of ocular discomfort
- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- BCVA
- Slit Lamp Biomicroscopy
- Corneal fluorescein staining
- Lissamine Green conjunctival staining
- IOP measurement
- Upon verification of study eligibility (Section 4), 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 (2 bottles) and instructions for administration
- [redacted]

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 the subjects. 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.

**Instructions to subject:**

- Dose investigational product as instructed
- [redacted]
- [redacted]
- Return for Visit 3 scheduled on Day 8 ± 1 day.

### 5.1.3. Visit 3: Day 8 ± 1 day – Diary Collection Visit

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

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- [redacted]
- Subject-rated assessment of ocular discomfort

**Instructions to subject:**

- Dose investigational product as instructed
- [redacted]
- [redacted]
- Return for Visit 4 scheduled on Day 15 ± 1 day.

### 5.1.4. Visit 4: Day 15 ± 1 day – Study Visit

This visit will occur on Day 15 ± 1 day as calculated from Visit 2: Day 1, and the following evaluations will be performed/assessed:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- [redacted]
- Used and unused double-masked investigational product collected, counted, and compliance assessed (via subject diary)
- Subject-rated assessment of ocular discomfort

- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- BCVA
- Slit Lamp Biomicroscopy:
- Corneal fluorescein staining
- Lissamine Green conjunctival staining
- IOP measurement
- Subject will receive a re-supply of double-masked investigational product to last until Visit 6.

**Instructions to subject:**

- Dose investigational product as instructed
- [redacted]
- Return for Visit 5 scheduled on Day 22 ± 1 day.

### 5.1.5. Visit 5: Day 22 ± 1 day – Diary Collection Visit

This visit will occur on Day 22 ± 1 day as calculated from Visit 2: Day 1, and the following evaluations will be performed:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- [redacted]
- Subject-rated assessment of ocular discomfort

**Instructions to subject:**

- Dose investigational product as instructed
- [redacted]
- Return for Visit 6 scheduled on Day 29 ± 1 day

### 5.1.6. Visit 6: Day 29 ± 1 day – End of Study Visit

The end-of-investigational-product-use visit will occur on Day 29 ± 1 day as calculated from Visit 2: Day 1, and the following will be performed/assessed:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- [redacted]
- Used and unused double-masked investigational product collected, counted, and compliance assessed (via subject diary)
- Subject-rated assessment of ocular discomfort
- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- BCVA
- Slit Lamp Biomicroscopy:
- Corneal fluorescein staining
- Lissamine Green conjunctival staining
- IOP measurement
- Dilated ophthalmoscopy
- UPT
- Release of subject from the study

### 5.1.7. Unscheduled Visit

Any visits or procedures performed beyond those specified within the protocol must be documented in the Unscheduled Visit pages of the 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 6 should be completed rather than the eCRFs for an Unscheduled Visit.

### 5.1.8. Early Termination Visit

In the event of termination prior to Visit 6, every attempt will be made to ensure that all Visit 6 assessments are performed. If this is not feasible, at least the following should be performed/assessed:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Used and unused investigational product collected and compliance [redacted]

- [redacted]
- BCVA
- Slit lamp biomicroscopy
- IOP measurement

## 5.2. RESCUE MEDICATION USE

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 6. Rescued subjects will be considered treatment failures, but 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.

## 5.3. SUBJECT WITHDRAWAL AND/OR DISCONTINUATION

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 6 assessments as possible. If a non-serious AE is unresolved at the time of the subject's final study visit, 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 all serious adverse events (SAEs) to resolution. The reason for premature discontinuation should be entered onto the Case Report Form (CRF) 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.

## 5.4. COLLECTION OF DATA

Source documentation for data collected in this study will be maintained at the investigative site. In cases where no source will be used [redacted] it will be noted in the Investigator files. The CRF will be electronic (eCRF) and data will be electronically entered from the source documentation into the eCRF. After study completion, an archival copy [e.g., Portable Document Format (PDF)] of the eCRF data will be retained by the site.

# 6. TREATMENT OF SUBJECTS

## 6.1. INVESTIGATIONAL PRODUCTS TO BE ADMINISTERED

All subjects meeting eligibility criteria at Visit 1 will receive 2 bottles of single-masked investigational product (vehicle). Subjects who continue to meet eligibility criteria at Visit 2 will be randomized to either KPI-121 0.25% ophthalmic suspension or vehicle. One kit of randomized investigational product containing 3 dropper bottles will be allocated to each subject at Visit 2. At Visit 2 (Day 1/Randomization), subjects will receive 2 bottles of double-masked investigational product (KPI-121 0.25% ophthalmic suspension or vehicle). At Visit 4 (Day 15 ± 1 day), subjects will receive 1 additional bottle of double-masked investigational product from the kit allocated. All bottles will be returned to the site at Visit 6 (Day 29 ± 1 day). The investigational product will be stored at the site in a secure area with limited access at controlled room temperature (15-25°C/59-77°F).

Subjects will be asked to administer investigational product QID. Prior to each instillation, subject will be instructed to shake investigational product bottle. The subjects will record the time of administration of each dose of investigational product at the time of instillation (Appendix 12). Compliance with instillation of investigational product will be reviewed and assessed at each clinic visit.

## 6.2. CONCOMITANT MEDICATIONS

All medications that the subject has taken 6 months prior to Visit 1 and through Visit 6 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 will be recorded for each medication.

### 6.2.1. Permitted Medications

Medications not specifically excluded in Section 6.2.2 may be taken as necessary.

### 6.2.2. Medications Not Permitted

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

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

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

- Ocular, inhaled, or intranasal corticosteroids
- Ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs)
- Topical ocular antibiotics
- Topical ocular antihistamines or mast cell stabilizers
- Oral antihistamines
- Topical or nasal vasoconstrictors
- Other investigational products

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

- Topical cyclosporine (Restasis®)
- 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
- Antidepressants
- Isotretinoin
- Oral corticosteroids
- Systemic immunosuppressive agents

## 6.3. INVESTIGATIONAL PRODUCT USE COMPLIANCE

Compliance will be assessed by comparing investigational product accountability records with the [redacted]. The site will document this comparison 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.

## 6.4. DRUG 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 drug 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 drug 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.

Investigational product will be stored at controlled room temperature (15-25°C/59-77°F) in an area limited to controlled access.

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 drug accountability. All drug accounting procedures must be completed before the study is considered complete.

### 6.5. MAINTENANCE OF RANDOMIZATION AND PROCEDURE FOR BREAKING THE CODE

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 at the CRO. 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.

# 7. ASSESSMENT OF EFFICACY

Efficacy assessments include the following:

- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted] severity assessment
- [redacted] frequency assessment
- Subject-rated assessment of ocular discomfort severity
- Subject-rated assessment of ocular discomfort frequency
- [redacted]
- Corneal fluorescein staining
- Lissamine green conjunctival staining

# 8. ASSESSMENT OF SAFETY

## 8.1. SAFETY PARAMETERS

Safety parameters include:

- Assessments of AEs
- BCVA
- Slit lamp biomicroscopy
- Dilated ophthalmoscopy
- IOP measurement

## 8.2. ADVERSE EVENT DEFINITIONS

**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 patient 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.

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 inpatient hospitalization.
- Prolongs inpatient 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.

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.

**Possible:**

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

**Probable:**

- 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.

**Definite:**

- 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.

## 8.3. PROCEDURES FOR AE REPORTING BY THE INVESTIGATOR

AEs will be monitored throughout the study and will be recorded on the CRF 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.

## 8.4. SERIOUS ADVERSE EVENT REPORTING BY THE INVESTIGATOR

**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
1. Site Number
2. Subject Number
3. Subject Demographic information, including:
    - Date of Birth
    - Sex
    - Race
4. Investigational product start date
5. Date of last dose of investigational product
6. Date investigational product reinitiated (if investigational product interrupted)
7. 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
8. 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 patient 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 inpatient hospitalization, or the development of drug dependency or drug abuse.
9. Concomitant medications
10. Relevant history

11. Possible causes of SAE other than investigational product
12. Copy of AE page from the CRF

**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.

# 9. STATISTICS

## 9.1. STATISTICAL METHODS

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.

### 9.1.1. Subject Disposition, Demographic and Background Characteristics

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

### 9.1.2. Analysis of Efficacy

The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all subjects randomized. A subset of efficacy analyses will be examined for the Efficacy Evaluable (EE) population, the definition of which will be outlined in the Statistical Analysis Plan and finalized prior to unmasking of study data pursuant to clinical data review.

The primary analysis of all ophthalmic efficacy measures will be based on the single study eye for each subject.

The co-primary endpoints are (1) the mean bulbar conjunctival hyperemia score at Visit 6; and (2) the mean [redacted] severity score averaged over the days from Visit 5 to the day before Visit 6.

Secondary and exploratory efficacy endpoints will be evaluated as elaborated in Section 3.

### 9.1.3. Analysis of Safety

Analysis of safety data will be presented for all subjects in the Safety population (i.e., all subjects receiving randomized investigational product). 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.

## 9.2. SAMPLE SIZE ESTIMATION

A sample size of 71 in each group will have 90% power to detect an effect size of [redacted] using a 2-group t-test with a [redacted] 2-sided significance level.

## 9.3. LEVEL OF SIGNIFICANCE

The primary assessment of the dose-response will be evaluated using a 5% level of significance. Since both co-primary endpoints will be required to be significant at the 0.05 level, there is no adjustment needed for multiple comparisons.

All other reported *p*-values will be considered descriptive and hypothesis generating.

## 9.4. PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, OR SPURIOUS DATA

Any missing, unused, or spurious data will be noted in the final clinical study report. 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). 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. Imputation will be carried out only on the co-primary endpoints and time points.

## 9.5. 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.

## 10. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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.

# 11. QUALITY CONTROL

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.

# 12. ETHICS

## 12.1. Institutional Review Board

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.

## 12.2. Informed Consent Requirements

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.

# 13. DATA HANDLING AND RECORDKEEPING

All procedures for the handling and analysis of data will be conducted using GCP and meet ICH guidelines and US FDA regulations for the handling and analysis of data for clinical trials.

## 13.1. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database. Query reports pertaining to data omissions and discrepancies will be forwarded to the clinical Investigator and monitor(s) for resolution. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.

## 13.2. Records Retention

The study center will retain all records related to the study in accordance with local and ICH GCP guidelines.

## 14. 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.

## 15. 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. Stevenson W, Chauhan SK, Dana R. Dry eye disease: An immune-mediated ocular surface disorder. *Arch Ophthalmol*. 2012;130(1):90-100. doi:10.1001/archophthalmol.2011.364.
3. Lane SS, Holland EJ. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. *J Cataract Refract Surg*. 2013;39(2):168-173. doi:10.1016/j.jcrs.2012.10.039.
4. [redacted]
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.

# 16. APPENDICES

## APPENDIX 1: SUMMARY OF EVENTS

| Procedures | Visit 1 Screening<br>14 ± 1 Days Prior to Day 1 | Visit 2 Randomization<br>Day 1 | Visit 3 [redacted]<br>Day 8 (±1 day) | Visit 4 Study Visit<br>Day 15 (±1 day) | Visit 5 [redacted]<br>Day 22 (±1 day) | Visit 6 End of Study Visit<br>Day 29 (±1 day) |
|---|---|---|---|---|---|---|
| Informed Consent, HIPAA Authorization and Medical History | X | | | | | |
| Concomitant medication query | X | X | X | X | X | X |
| UPT[a] | X | | | | | X |
| Inclusion/Exclusion | X | X | | | | |
| AE Assessment | X | X | X | X | X | X |
| Subject-rated assessment of ocular discomfort | X | X | X | X | X | X |
| [redacted] | X | X[c] | X[c] | X[c] | X[c] | X[c] |
| Investigator-rated assessment of bulbar conjunctival hyperemia | X | X | | X | | X |
| [redacted] | | X | | X | | X |
| BCVA | X | X | | X | | X |
| Slit lamp biomicroscopy | X | X | | X | | X |
| Corneal fluorescein staining | X | X | | X | | X |
| Lissamine Green conjunctival staining | X | X | | X | | X |
| Unanesthetized Schirmer Test Assessment | X | | | | | |
| IOP measurement | X | X | | X | | X |
| Dilated ophthalmoscopy | X | | | | | X |

| Procedures | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|---|---|---|---|---|---|---|
| Investigational product administration in-clinic | X[b] | X | | | | |
| Dispense investigational product | X[b] | X | | X | | |
| [redacted] | X[b] | X | X | X | X | |
| Collect investigational product | | X[b] | | | | X |
| [redacted] | | X[b] | X | X | X | X |

[a]Women of childbearing potential only; [b]Run-In Product [redacted]

## APPENDIX 2: SUBJECT-RATED OCULAR DISCOMFORT ASSESSMENT

Subjects will be asked to subjectively rate their ocular discomfort severity and frequency at Visits 1-6. Investigator site designees will ask the subject the following question and record their answer in the eCRF. This assessment is a general assessment of both eyes. There will not be a question for each individual eye.

### Severity of Symptoms

On average over the past day, how would you rate the severity of your ocular discomfort associated with dry eye (for example, dryness or irritation)?

0 = None

1 = Mild

2 = Moderate

3 = Severe

4 = Very Severe

### Frequency of Symptoms

On average over the past day, how often have you had this level of ocular discomfort associated with dry eye (for example, dryness or irritation)?

0 = Never

1 = Sometimes

2 = Often

3 = Constantly

## APPENDIX 3: [redacted] ASSESSMENT

Subjects will be asked to subjectively rate their ocular discomfort severity and frequency at Visit 1 for eligibility. [redacted] The total length of the line from [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.

### [redacted] 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]

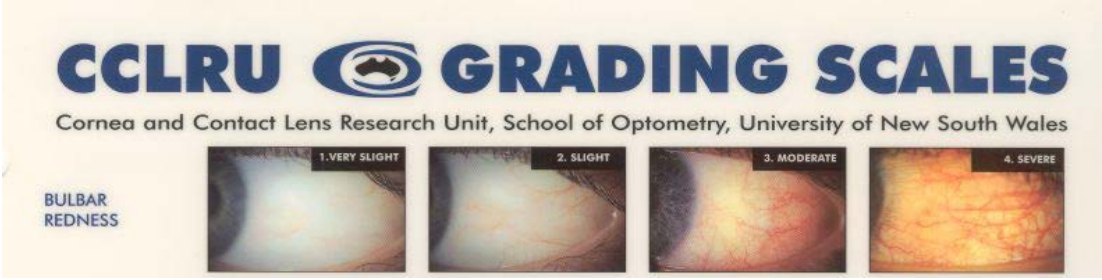
### [redacted] FREQUENCY ASSESSMENT

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: INVESTIGATOR-RATED ASSESSMENT OF BULBAR CONJUNCTIVAL HYPEREMIA

Investigators will rate bulbar conjunctival hyperemia at Visits 1, 2, 4, and 6 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. 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 notched end of the unanesthetized Schirmer Test strip at the apex of "v". 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 sharp pencil 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, 4 and 6.

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*: logMAR VA = Baseline value + (n X 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, 4 and 6. 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 the 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

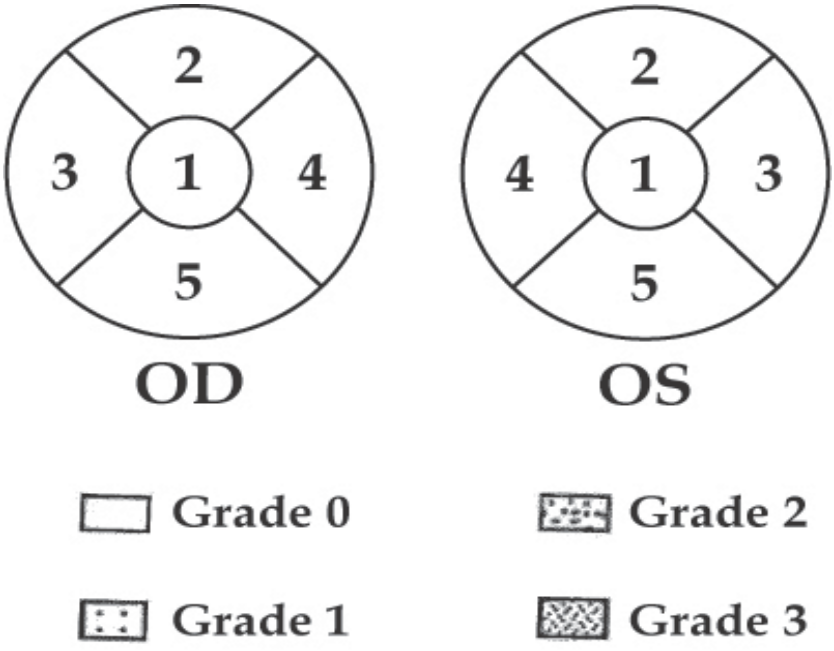
Corneal staining will be performed at Visit 1, 2, 4, and 6. Corneal staining assessment will be performed using methods developed by the NEI Dry Eye Workshop[5,6].

**Evaluation Technique**

1. Place magnification at 16x
2. Use a yellow barrier filter (Wratten or Tiffen #11 or #12)
3. Place 5 µl of non-preserved, 2% fluorescein into eye using a 2-20µl micropipette fitted with a clean pipette tip.
4. Gently touch the drop at the tip to the lower palpebral conjunctiva of the right eye.
5. In order to thoroughly mix the fluorescein with the tear film, ask the subject to blink several times and move his/her eye around.
6. Wait 2.5 minutes to assess cornea
7. Measure staining under Cobalt blue light (465 nm to 490 nm)
8. Compare staining with standard with scoring in each of 5 areas 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 micopunctate or macropunctate staining within the section of cornea being evaluated

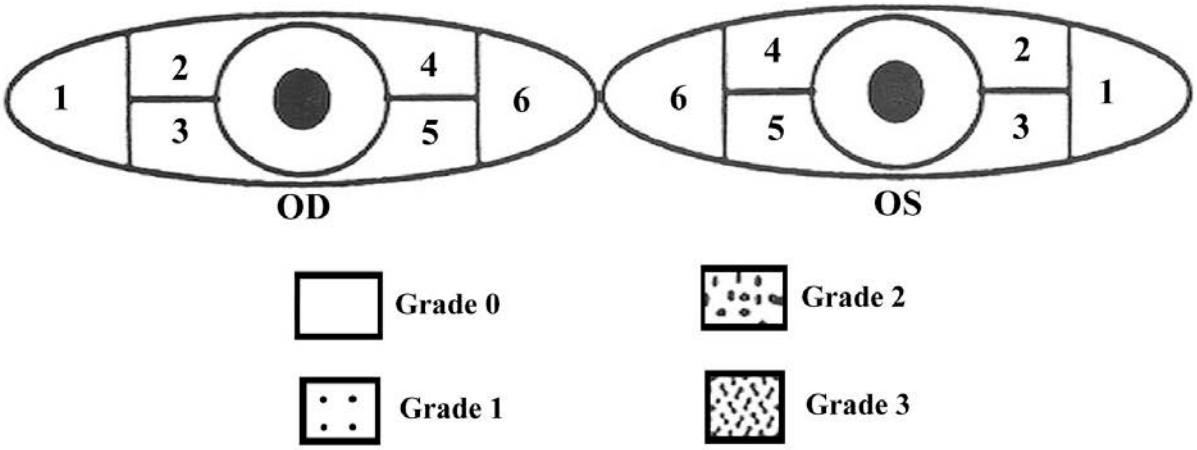

2
3
1
4
5
OD
2
4
1
3
5
OS
Grade 0
Grade 2
Grade 1
Grade 3

## APPENDIX 9: LISSAMINE GREEN CONJUNCTIVAL STAINING

Lissamine Green staining will be performed at Visit 1, 2, 4, and 6.

The conjunctiva will be stained with non-preserved, 1% lissamine green. When conducting all assessments room temperature and humidity should be relatively consistent throughout each visit and throughout the study.

- Without flushing the eye from the previous assessment, instill a 20 µl drop of lissamine green to the right eye using a micropipette, allowing a drop to form.
- Gently touch the drop at the tip of the delivery dropper to the lower palpebral conjunctiva of the right eye.
- In order to thoroughly coat the ocular surface with the lissamine, ask the subject to blink several times and move his/her eye around.
- After 1 minute and before 4 minutes have elapsed, using white light of moderate intensity, grade the areas of the conjunctiva of the right eye with the 0-3 scale shown below.
- Staining induced by Schirmer Test strip should be excluded.
- Repeat this procedure for the left eye.



## APPENDIX 10: IOP MEASUREMENT

IOP measurements will be performed utilizing Goldmann applanation tonometery according to the Investigator's standard procedure. All pressure will be recorded in mmHg. IOP assessments will occur at study Visits 1, 2, 4, and 6.

## APPENDIX 11: 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 and Visit 6 after to 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, the Investigator will determine whether or not the abnormality would exclude subject from study participation.

[redacted]

[redacted]

[redacted]

[redacted]