NCT02218489

Study ID:
KPI-121-C-003

Study Title:
A Phase 2, Double-Masked, Randomized, Vehicle-Controlled Study to Evaluate the Effect of KPI-121 0.25% Ophthalmic Suspension on Signs and Symptoms of Inflammatory Meibomian Gland Disease

Date:
03 Nov 2015

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-003

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Sponsor:	Kala Pharmaceuticals, Inc. 100 Beaver St, Suite 201 Waltham, MA 02453
Medical Monitor:	[redacted]
Issue Date:	Original: 16 Jun 2014 Clarification Letter: 03 Jul 2014 Amendment 1: 11 Jul 2014 Amendment 2: 07 Aug 2014 Clarification Letter: 28 Aug 2014 Amendment 3: 12 Sep 2014 Amendment 4: 12 Nov 2014 Amendment 5: 10 Dec 2014 Amendment 6: 12 Jun 2015 Amendment 7: 12 Aug 2015 Amendment 8: 03 Nov 2015
Approved:	03 Nov 2015

[redacted]

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-003
Investigator Signature Page

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Contact for Serious Adverse Events:	[redacted]

Investigator Name (printed or typed):

_____

Investigator's Signature:

_____ _____
Date

SYNOPSIS

Study Title:	KPI-121-C-003: A Phase 2, Double-Masked, Randomized, Vehicle-Controlled Study to Evaluate the Effect of KPI-121 0.25% Ophthalmic Suspension on Signs and Symptoms of Inflammatory Meibomian Gland Disease
Objectives:	The primary objective of this study is to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects with signs and symptoms of inflammatory meibomian gland disease (MGD).
Study Population:	The study population will consist of subjects with mild to moderate inflammatory MGD.
Number of Subjects:	Up to 750 subjects who are diagnosed with inflammatory MGD will be screened. From those screened, approximately 200 subjects will be randomized to KPI-121 0.25% ophthalmic suspension or vehicle.
Investigational Products:	KPI-121 0.25% ophthalmic suspension or 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 30 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 in subjects with inflammatory MGD. Approximately 750 subjects will be screened and up to 200 subjects will be randomized at up to 12 centers located in the United States (US). After a run-in period of treatment with vehicle, 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 30 days or 2) vehicle administered as 1-2 drops in each eye QID for up to 30 days. Furthermore, subjects will be assigned to a study arm based on the stratification of:

	• Subject's Visit 1 (Day -14) [redacted] AND • Visit 1 (Day -14) investigator-rated posterior lid margin hyperemia score [redacted] 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. At Visit 2 Randomization (Day 1), subjects who continue to meet inclusion/exclusion criteria (with the exception of Inclusion Criteria #4 and #7) will be eligible for randomization to KPI-121 0.25% ophthalmic suspension or vehicle. Following randomization, subjects will return to the clinic for evaluation at Study Visit 3 (Day 8 ± 1 day), Visit 4 (Day 15 ± 1 day), Visit 5 (Day 22 ± 1 day) and Visit 6 (Day 29 ± 1 day). At Visits 3 (Day 8 ± 1 day) and 5 (Day 22 ± 1 day) evaluations will include [redacted] and subject-rated assessment of ocular discomfort. A complete study evaluation will be conducted at Study Visits 4 and 6. Subjects will be released from the study at the end of Visit 6 (Day 29 ± 1 day). Assessments will include • Investigator-rated assessment of posterior lid margin hyperemia • [redacted] • Investigator-rated assessment of conjunctival hyperemia • Investigator-rated assessment of the character of the meibomian glands' contents • Investigator-rated assessment of the expressibility of the meibomian glands • Tear film break up time (TFBUT) • Corneal fluorescein staining

	• [redacted] discomfort assessment • In-clinic subject-rated assessment of ocular discomfort • Best corrected visual acuity (BCVA) • Slit lamp biomicroscopy • Intraocular pressure (IOP) measurement • Dilated ophthalmoscopy
Efficacy Endpoints	**Primary Efficacy Endpoints:** Comparison of mean [redacted] Severity Assessment Score between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 (based on the mean score for the 3 days prior to Visit 4) Comparison of mean posterior lid margin hyperemia [redacted] at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 **Secondary Efficacy Endpoints:** Comparison of mean [redacted] Severity Assessment Score between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 6 (based on the mean score for the 3 days prior to Visit 6) Comparison of mean posterior lid margin hyperemia [redacted] at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 6

	[redacted] **Exploratory Endpoints:** Comparison of mean investigator-rated assessment of conjunctival hyperemia between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 • Visit 6 Comparison of mean investigator-rated character of the meibomian glands' contents between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 • Visit 6 Comparison of mean investigator-rated expressibility of the evaluated meibomian glands between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 • Visit 6 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 TFBUT between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 • Visit 6 Comparison of mean [redacted] Frequency Assessment Score between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

	• Visit 4 (based on the mean score for the 3 days prior to Visit 4) • Visit 6 (based on the mean score for the 3 days prior to Visit 6) Comparison of mean change from baseline (Visit 2) in posterior lid margin hyperemia [redacted] for subjects with greater than or equal to a grade of 1 in at least one posterior lid margin (i.e., RUL, LUL, RLL, LLL) at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 as compared to Visit 2 • Visit 6 as compared to Visit 2 [redacted] Comparison of mean change from baseline (Visit 2) investigator-rated assessment of conjunctival hyperemia between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 as compared to Visit 2 • Visit 6 as compared to Visit 2 Comparison of mean change from baseline (Visit 2) investigator-rated assessment of the character of the meibomian glands' contents between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 as compared to Visit 2 • Visit 6 as compared to Visit 2 Comparison of mean change from baseline (Visit 2) between investigator-rated assessment of the expressibility of the meibomian glands the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 as compared to Visit 2 • Visit 6 as compared to Visit 2

	Comparison of mean change from baseline (Visit 2) corneal fluorescein staining between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 as compared to Visit 2 • Visit 6 as compared to Visit 2 Comparison of mean change from baseline (Visit 2) TFBUT between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 as compared to Visit 2 • Visit 6 as compared to Visit 2 Comparison of mean change from baseline (Visit 2) [redacted] Severity Assessment Score between the KPI-121 0.25% ophthalmic suspension group and the vehicle group: • Visit 4 (based on the mean score for the 3 days prior to Visit 4 and Visit 2) • Visit 6 (based on the mean score for the 3 days prior to Visit 6 and Visit 2) Comparison of mean change from baseline (Visit 2) [redacted] Frequency Assessment Score between the KPI-121 0.25% ophthalmic suspension group and within the vehicle group: • Visit 4 (based on the mean score for the 3 days prior to Visit 4 and Visit 2) • Visit 6 (based on the mean score for the 3 days prior to Visit 6 and Visit 2) Comparison of the mean [redacted] Severity Assessment Score between KPI-121 0.025% ophthalmic suspension group and the vehicle group • Visit 4 (based on the mean score for the day prior to Visit 4) • Visit 6 (based on the mean score for the day prior to Visit 6) Comparison of the mean change from baseline (Visit 2) [redacted] Severity Assessment Score between KPI-121 0.025% ophthalmic suspension group and the vehicle group

	• Visit 4 (based on the mean score for the day prior to Visit 4 and Visit 2) • Visit 6 (based on the mean score for the day prior to Visit 6 and Visit 2)
Safety Endpoints	• IOP measurements • Slit-lamp Biomicroscopy • BCVA • Ophthalmoscopy • Adverse Event (AE) monitoring
Eligibility Criteria:	**Inclusion Criteria:** At Visit 1 and Visit 2, individuals of either gender or any race will be eligible for study participation if they: 1. Provide written informed consent and Health Insurance Portability and Accountability Act (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. In addition, they must demonstrate: a. Single-masked investigational product use compliance of at least 80% during the final week of the run-in phase AND b. [redacted] compliance of at least 80% in the final week of the run-in phase. 4. Upon examination at **Visit 1 ONLY**, have **ALL 5** of the following criteria in the **same** or **both** eyes: a. [redacted]

	e. An **unanesthetized Schirmer** score [redacted] 5. Are women of child bearing potential (WOCBP), who are not pregnant or lactating and not sexually active (i.e., abstinent) for 14 days prior to Visit 1 and are 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 one of the following acceptable methods of birth control for the times specified: a. Intrauterine device (IUD) in place for at least 3 months prior to Visit 1 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 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 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 for 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. 6. Are postmenopausal women, who have had no menstrual cycle for at least 1 year prior to Visit 1 or have undergone one 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 **Exclusion Criteria:** In order for subjects to be eligible at Visit 1 and Visit 2 they may not: 1. Have 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) and 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 low dose aspirin (≤ 81 mg per day) 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 days prior to Screening (Visit 1) and for the duration of the study: a. Topical cyclosporine (Restasis®) b. Any form of topical loteprednol etabonate (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 and 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 of tumor necrosis factor (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, have history of or current glaucoma, or an IOP over 21mmHg at Visit 1 (Screening) or Visit 2 (Randomization). 9. Initiate or alter the use (if using upon entry) of oral contraceptives, or female hormone replacement therapy/supplementation within 48 hours prior to Visit 1 and for the duration of the study. 10. Be unwilling to abstain from wearing contact lenses for 14 days prior to Visit 1 and throughout the study. 11. 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). 12. Be unwilling to discontinue warm compress therapy, lid expression, or lid massage 14 days prior to Day 1 and for the duration of the study. 13. 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. Rosacea with corneal involvement.

	g. Severe/serious ocular condition that in the judgment of the investigator could confound study assessments or limit compliance. h. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance. 14. Have concurrent acute hordeolum (stye) or chalazion. 15. Have significant anterior blepharitis, significant dandruff, or *Demodex follicularum* infestation. 16. Have complete obstruction of the meibomian glands evaluated that present with no expressibility. 17. Have concurrent signs of moderate to severe chronic eyelid margin inflammation (moderate to severe eyelid margin telangiectasia and eyelid margin scarring) or lid structural abnormalities such as entropion, ectropion, trichiasis, or lash loss. 18. Have had ocular surgery in the past 90 days or require ocular surgery during the study. 19. Have active or have had an outbreak of herpetic keratitis within 1 year of Visit 1. 20. Have used eye make-up (e.g., eyeliner, mascara, eye shadow, eyelid glitter, eyelid concealer or base), eyelash curlers, eyelid glue, or false eyelashes at Visit 1 or are unwilling to discontinue the use of these products on the days of study visits. 21. Have permanent eyeliner. 22. Have a documented 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. 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. 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.
LE	Loteprednol etabonate
LLL	Left Lower Lid
LUL	Left Upper Lid
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MGD	Meibomian Gland Disease
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
MPP	Mucus Penetrating Particles
NDA	New Drug Application
NEI	National Eye Institute
NSAID	Nonsteroidal Anti-inflammatory Drug
PDF	Portable Document Format
RLL	Right Lower Lid

RUL	Right Upper Lid
QID	Four Times Daily
SAE	Serious Adverse Event
[redacted]	[redacted]
SAR	Suspected Adverse Reaction
SOP	Standard Operating Procedure
TFBUT	Tear Film Break-up Time
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

Meibomian gland dysfunction (MGD), the most common type of evaporative dry eye, is a disorder in which meibomian glands either hypersecrete or are obstructed (DEWS Report, 2007). According to Geerling[1], MGD is highly under diagnosed and undertreated. The role of functioning meibomian glands in achieving an optimal ocular surface, and thus good overall vision, is often misunderstood[1]. Many are not aware of the quality of life issues associated with MGD, including red, puffy eyes and discomfort[1].

Over 7 million people in the United States experience dry eye symptoms of some severity, some of which include the sub-type of MGD[2]. 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, including MGD, may experience significant ocular discomfort and reduced visual function, thus resulting in a decreased quality of life or work productivity[2].

Current treatments for MGD vary widely, and can include massage and lid expression as well as tetracycline and doxycycline, though these are generally considered to be only mildly effective[3]. Another option is topical cyclosporine (Restasis®), the only prescription medication currently approved by the Food and Drug Administration (FDA) 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[4]. Factors adversely affecting tear film stability and osmolarity can initiate an inflammatory cascade that leads to the development of a self-perpetuating inflammatory cycle[4]. 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[5].

Loteprednol etabonate (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. 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 MGD. Study KPI-121-C-003 will evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension in subjects with MGD. Additional information about KPI-121, including nonclinical pharmacology study results, and potential risks and benefits to human subjects, is 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 ocular inflammatory disease including inflammatory MGD.

KPI-121 0.25% ophthalmic suspension contains 0.25% (w/v) LE in an essentially 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 except it 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 will 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 signs and symptoms of inflammatory MGD.

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 750 subjects with mild to moderate inflammatory MGD will be screened for this study. Approximately 200 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 this study is to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects with signs and symptoms of inflammatory MGD.

3. TRIAL DESIGN

3.1. PRIMARY EFFICACY ENDPOINTS

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

- Visit 4 (based on the mean score for the 3 days prior to Visit 4)

Comparison of mean posterior lid margin hyperemia [redacted] at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4

3.2. SECONDARY EFFICACY ENDPOINTS

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

- Visit 6 [redacted]

Comparison of mean posterior lid margin hyperemia [redacted] at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 6

[redacted]

3.3. EXPLORATORY EFFICACY ENDPOINTS

Comparison of mean investigator-rated assessment of conjunctival hyperemia between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

Comparison of mean investigator-rated character of the meibomian glands' contents between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

Comparison of mean investigator-rated expressibility of the evaluated meibomian glands between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

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 TFBUT between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4
- Visit 6

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

- Visit 4 [redacted]
- Visit 6 [redacted]

Comparison of mean change from baseline (Visit 2) in posterior lid margin hyperemia [redacted] for subjects with greater than or equal to a grade of 1 in at least one posterior lid margin (i.e., RUL, LUL, RLL, LLL) at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

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

[redacted]

Comparison of mean change from baseline (Visit 2) investigator-rated assessment of conjunctival hyperemia between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

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

Comparison of mean change from baseline (Visit 2) investigator-rated assessment of the character of the meibomian glands' contents between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

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

Comparison of mean change from baseline (Visit 2) between investigator-rated assessment of the expressibility of the meibomian glands the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

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

Comparison of mean change from baseline (Visit 2) corneal fluorescein staining between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

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

Comparison of mean change from baseline (Visit 2) TFBUT between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

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

Comparison of mean change from baseline (Visit 2) [redacted] Severity Assessment Score between the KPI-121 0.25% ophthalmic suspension group and the vehicle group:

- Visit 4 [redacted]
- Visit 6 [redacted]

Comparison of mean change from baseline (Visit 2) [redacted] Frequency Assessment Score between the KPI-121 0.25% ophthalmic suspension group and within the vehicle group:

- Visit 4 [redacted]
- Visit 6 [redacted]

Comparison of the mean [redacted] Severity Assessment Score between KPI-121 0.025% ophthalmic suspension group and the vehicle group

- Visit 4 [redacted]
- Visit 6 [redacted]

Comparison of the mean change from baseline (Visit 2) [redacted] Severity Assessment Score between KPI-121 0.025% ophthalmic suspension group and the vehicle group

- Visit 4 [redacted]
- Visit 6 [redacted]

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]	[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]			[redacted]
[redacted] **Assessment of Posterior Lid Hyperemia**	Mean values	4	X		
[redacted] **Assessment of Posterior Lid Hyperemia**	Mean values	6		X	
[redacted] **Assessment of Posterior Lid Hyperemia**	Mean change from BL	4 vs. 2			X
[redacted] **Assessment of Posterior Lid Hyperemia**	Mean change from BL	6 vs. 2			X
Investigator-Rated Assessment of Bulbar Conjunctival Hyperemia	Mean values	4			X
Investigator-Rated Assessment of Bulbar Conjunctival Hyperemia	Mean values	6			X
Investigator-Rated Assessment of Bulbar Conjunctival Hyperemia	Mean change from BL	4 vs. 2			X

Evaluation	Comparison	Visit	1°	2°	Exploratory
Investigator-Rated Assessment of Bulbar Conjunctival Hyperemia	Mean change from BL	6 vs. 2			X
[redacted] **Severity**	Mean values	4 [redacted]	X		
[redacted] **Severity**	Mean values	6 [redacted]		X	
[redacted] **Severity**	Mean change from BL	4 [redacted]			X
[redacted] **Severity**	Mean change from BL	6 [redacted]			X
[redacted] **Severity**	Mean values	4 [redacted]			X
[redacted] **Severity**	Mean values	6 [redacted]			X
[redacted] **Severity**	Mean change from BL	4 [redacted]			X
[redacted] **Severity**	Mean change from BL	6 [redacted]			X

Evaluation	Comparison	Visit	1°	2°	Exploratory
[redacted] **Frequency**	Mean values	4 [redacted]			X
[redacted] **Frequency**	Mean values	6 [redacted]			X
[redacted] **Frequency**	Mean change from BL	4 [redacted]			X
[redacted] **Frequency**	Mean change from BL	6 [redacted]			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
Investigator-Rated Assessment of the Character of the Meibomian Glands' Contents	Mean values	4			X
Investigator-Rated Assessment of the Character of the Meibomian Glands' Contents	Mean values	6			X

Evaluation	Comparison	Visit	1°	2°	Exploratory
Investigator-Rated Assessment of the Character of the Meibomian Glands' Contents	Mean change from BL	4 vs. 2			X
Investigator-Rated Assessment of the Character of the Meibomian Glands' Contents	Mean change from BL	6 vs. 2			X
Investigator-Rated Assessment of the Expressibility of the Meibomian Glands	Mean values	4			X
Investigator-Rated Assessment of the Expressibility of the Meibomian Glands	Mean values	6			X
Investigator-Rated Assessment of the Expressibility of the Meibomian Glands	Mean change from BL	4 vs. 2			X
Investigator-Rated Assessment of the Expressibility of the Meibomian Glands	Mean change from BL	6 vs. 2			X
TFBUT	Mean values	4			X
TFBUT	Mean values	6			X
TFBUT	Mean change from BL	4 vs. 2			X
TFBUT	Mean change from BL	6 vs. 2			X

3.4. SAFETY ENDPOINTS

- IOP measurements
- Slit-lamp biomicroscopy
- BCVA
- Ophthalmoscopy
- AE monitoring

3.5. DESCRIPTION OF TRIAL 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 in subjects with inflammatory MGD.

This study will include up to 6 clinic visits, including 2 weeks of single-masked vehicle run-in followed by up to 30 days of investigational product dosing (KPI-121 0.25% ophthalmic suspension or vehicle).

Up to 750 subjects at up to 12 centers located in the United States (US) will be screened at Visit 1 (Screening). Subject meeting eligibility criteria will enter a 14-day run-in period of QID dosing (1-2 drops per eye of single-masked vehicle). Approximately 200 subjects will be randomized to KPI-121 0.25% ophthalmic suspension or vehicle.

At Visit 2, subjects who continue to meet inclusion/exclusion criteria (with the exception of Inclusion Criteria #4 and #7) will be randomized in an approximate 1:1 ratio to either 1) KPI-121 0.25% ophthalmic suspension administered as 1-2 drops in each eye QID for up to 4 weeks or 2) vehicle administered as 1-2 drops in each eye QID for up to 4 weeks.

The study eye will be selected based on the qualification criteria entered into the Interactive Web Response System (IWRS) for stratification at randomization. These scores are based on findings at Visit 1 only. If both eyes qualify for the study, the study eye will be designated as OD. Randomization numbers will be assigned to subjects as they are entered into the IWRS, based on the following 2 stratification criteria:

- Subject's Visit 1 (Day -14) [redacted] score [redacted] AND
- Visit 1 (Day -14) investigator-rated posterior lid margin hyperemia score [redacted]

The IWRS will assign masked study kit numbers, and bottles of investigational product will be dispensed at designated visits. The Sponsor, Investigators, and study staff will be masked during the randomization process and throughout the remainder of the study.

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

[redacted]

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

- In-clinic subject-rated assessment of ocular discomfort (Appendix 2)
- [redacted] severity and frequency assessments (Appendix 3)
- Investigator-rated assessment of posterior lid margin hyperemia (Appendix 4)
- Investigator-rated assessment of the character of the content of meibomian glands (Appendix 4)
- Investigator-rated assessment of expressibility of meibomian glands (Appendix 4)
- Investigator-rated assessment of conjunctival hyperemia (Appendix 5)
- Unanesthetized Schirmer Test (Appendix 6)
- BCVA (Appendix 7)
- Slit lamp biomicroscopy (Appendix 8)
- Corneal fluorescein staining (Appendix 9)
- IOP measurement (Appendix 10)
- Dilated ophthalmoscopy (Appendix 11)
- [redacted]
- [redacted]
- TFBUT (Appendix 14)

A study schematic follows (Figure 1).

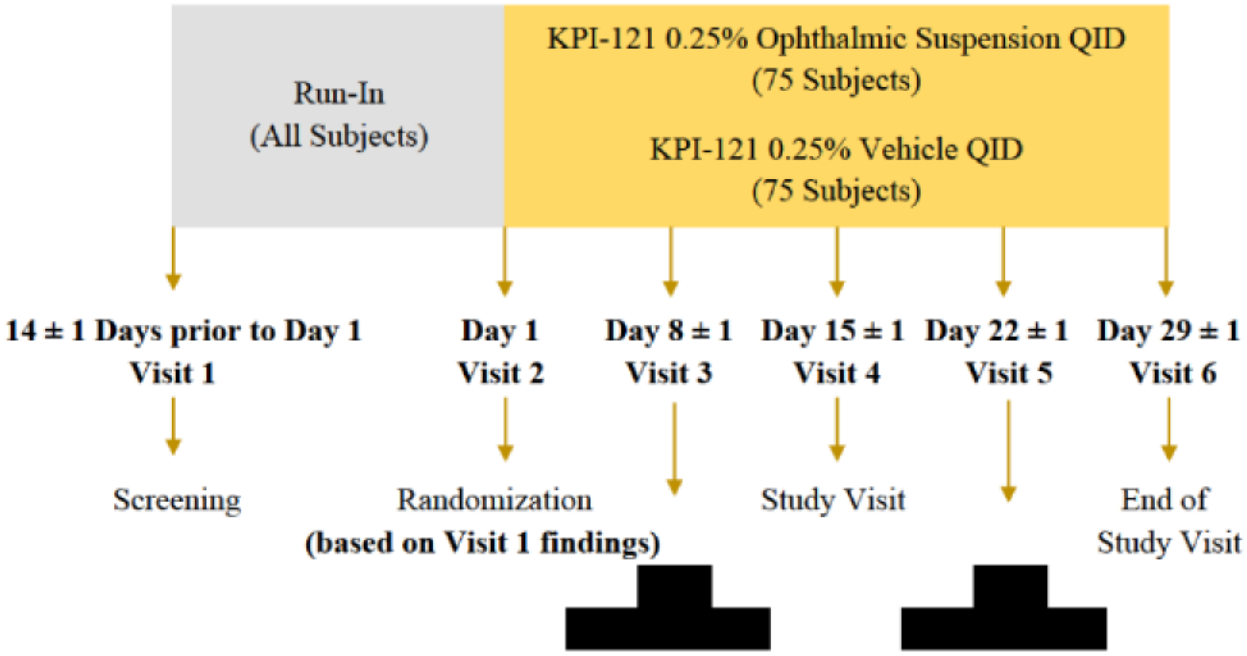


FIGURE 1: STUDY SCHEMATIC

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.

Subjects 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 from a common site level supply. The bottle labels for the singe-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 containing 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). At Visits 1 and 2, when subjects receive the first dose in the clinic, that dose will count as 1 of their 4 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 of 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, the following measures will be taken:

- Investigational product allocation (KPI-121 0.25% ophthalmic suspension versus vehicle) will be randomized and masked to the sponsor, subjects, and select investigative staff.
- 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 CRITERIA

At Visit 1 and Visit 2, 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. In addition, they must demonstrate:
    a. Single-masked investigational product use compliance of at least 80% during the final week of the run-in phase AND
    b. Diary completion compliance of at least 80% in the final week of the run-in phase.
4. Upon examination at **Visit 1 ONLY**, have **ALL 5** of the following criteria in the **same** or **both** eyes:
    a. [redacted] **Severity Assessment**.
    e. An **unanesthetized Schirmer** score [redacted]
5. Are women of child bearing potential (WOCBP), who are not pregnant or lactating and not sexually active (i.e., abstinent) for 14 days prior to Visit 1 and are 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 one 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 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 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 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 for 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.

6. Are postmenopausal women, who have had no menstrual cycle for at least 1 year prior to Visit 1 or have undergone one 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

4.2. SUBJECT EXCLUSION CRITERIA

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

1. Have 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) and for the duration of the study:
   a. Ocular, inhaled, or intranasal corticosteroids
   b. Ocular or oral NSAIDs with the exception of low dose aspirin (≤ 81 mg per day)
   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 days prior to Screening (Visit 1) and 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 of TNF-blocking agents (e.g. etanercept, adalimumab, infliximab) at Visit 1 (Screening) and for the duration of the study.
8. Be currently receiving treatment for glaucoma, have history of or current glaucoma, or an IOP over 21mmHg at Visit 1 (Screening) or Visit 2 (Randomization).
9. Initiate or alter the use (if using upon entry) of oral contraceptives, or female hormone replacement therapy/supplementation within 48 hours prior to Visit 1 and for the duration of the study.
10. Be unwilling to abstain from wearing contact lenses for 14 days prior to Visit 1 and throughout the study.
11. Be monocular or have a BCVA, using corrective lenses if necessary, of +1.0 logMAR or worse as assessed by ETDRS.
12. Be unwilling to discontinue warm compress therapy, lid expression, or lid massage 14 days prior to Day 1 and for the duration of the study.
13. 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. Rosacea with corneal involvement.
   g. Severe/serious ocular condition that in the judgment of the investigator could confound study assessments or limit compliance.

h. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the investigator could confound study assessments or limit compliance.

14. Have concurrent acute hordeolum (stye) or chalazion.
15. Have significant anterior blepharitis, significant dandruff, or *Demodex follicularum* infestation.
16. Have obstruction of meibomian glands that present with no expressibility.
17. Have concurrent signs of moderate to severe chronic eyelid margin inflammation (moderate to severe eyelid margin telangiectasia and eyelid margin scarring) or lid structural abnormalities such as entropion, ectropion, trichiasis, or lash loss.
18. Have had ocular surgery in the past 90 days or require ocular surgery during the study.
19. Have active or have had an outbreak of herpetic keratitis within 1 year of Visit 1.
20. Have used eye make-up (e.g., eyeliner, mascara, eye shadow, eyelid glitter, eyelid concealer or base), eyelash curlers, eyelid glue, or false eyelashes at Visit 1 or are unwilling to discontinue the use of these products on the days of study visits.
21. Have permanent eyeliner.
22. Have a documented 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.
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. 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 DESCRIPTIONS

5.1.1. Visit 1: 14 ± 1 Days Prior to Day 1 – Screening

After site staff obtains written informed consent and HIPAA authorization, each subject 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. The following will be performed/assessed in order to determine initial eligibility for study participation:

- Non-ocular and ocular medical history
- Concomitant medication usage and medications taken during the 6 months prior to screening
- Urine pregnancy test (UPT) for WOCBP
- Subject-rated assessment of ocular discomfort
- [redacted]
- Investigator-rated assessment of signs
- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- TFBUT
- Corneal fluorescein staining
- Unanesthetized Schirmer Test evaluation
- BCVA
- Slit-lamp biomicroscopy
- IOP measurement
- Dilated ophthalmoscopy
- Review of inclusion and exclusion criteria to determine screening eligibility
- Dosing of run-in investigational product in clinic
- Dispensing of investigational product
- [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 on the first day.

Instructions to subject:

- Dose 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 day after Visit 1 (Screening). Subjects should dose run-in investigational product in both eyes QID until the Visit 2: Day 1 (Randomization).

The following will be performed/assessed at Visit 2:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Subject-rated ocular discomfort assessment
- Investigator-rated assessment of signs
- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- TFBUT
- Corneal fluorescein staining
- BCVA
- Slit-lamp biomicroscopy
- IOP measurement
- [redacted]
- Unused run-in investigational product collected, counted, and compliance assessed [redacted]
- Upon verification of subject eligibility (Section 4 with the exception of Inclusion Criteria #4 and #7), randomization of appropriate subjects to receive QID dosing of either KPI-121 0.25% ophthalmic suspension or vehicle.
- Dosing of randomized investigational product in clinic
- Dispensing of randomized investigational product
- [redacted]

The first dose of double-masked investigational product will be taken in the clinic under the supervision of a designated dosing coordinator. This dosing coordinator, who is not responsible for study assessments, will also be required to dispense and retrieve investigational product to/from the subjects. Prior to dosing, subjects will be instructed regarding proper method for instillation of their assigned investigational product including but not limited to shaking the 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 on Day 8 ± 1 day.

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

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
- Subject-rated assessment of ocular discomfort
- [redacted]
- Used and unused double-masked investigational product counted and compliance assessed [redacted]
- [redacted]

Instructions to subject:

- Dose investigational product as instructed.
- [redacted]
- [redacted]
- Return for Visit 4 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 [redacted]
- Subject-rated ocular discomfort assessment
- Investigator-rated assessment of signs
- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- TFBUT
- Corneal fluorescein staining
- BCVA
- Slit-lamp biomicroscopy
- IOP measurement
- Re-supply of double-masked investigational product to last until Visit 6.
- [redacted]

Instructions to subject:

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

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

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
- Subject-rated assessment of ocular discomfort
- [redacted]

- Used and unused double-masked investigational product counted and compliance assessed [redacted]
- [redacted]

Instructions to subject:

- Dose investigational product as instructed.
- [redacted]
- [redacted]
- Return for Visit 5 on Day 29 ± 1 day.

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

The End of Study 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
- UPT for WOCBP
- [redacted]
- Used and unused double-masked investigational product collected, counted, and compliance assessed [redacted]
- Subject-rated assessment of ocular discomfort
- Investigator-rated assessment of signs
- Investigator-rated assessment of bulbar conjunctival hyperemia
- [redacted]
- TFBUT
- Corneal fluorescein staining
- BCVA
- Slit-lamp biomicroscopy
- IOP measurement
- Dilated ophthalmoscopy
- [redacted]
- 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 assessed [redacted]
- Subject-rated assessment of ocular discomfort
- 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 discontinue investigational product use or withdraw from participation in the study for any reason is entitled to do so without obligation. The Investigator may also discontinue any subject from 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 the 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 (e.g., subject diary), it will be noted in the Investigator files. The CRF will be electronic (eCRF) and data will be entered from 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 the 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 and Therapies

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

6.2.2. Medications and Procedures Not Permitted

The following procedures and medications are not allowed for the time periods specified.

Within 14 ± 1 days prior to Visit 1 (Screening) and for the duration of the study:

- Warm compresses
- Lid margin expression

- Lid margin massage

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

- Eyelash growth medications
- Eye drops, gels, or artificial tears (including glaucoma medications)
- Any other topical ophthalmic medication
- TNF-blocking agents (e.g. etanercept, adalimumab, infliximab)

Within 48 hours prior to Visit 1 (Screening) and for the duration of the study, initiate or alter use of:

- Oral contraceptives, and female hormone replacement therapy/supplementation

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

- Ocular, inhaled, or intranasal corticosteroids
- Ocular or oral NSAIDs with the exception of low dose aspirin (≤ 81 mg per day)
- Topical ocular antibiotics
- Topical ocular antihistamines or mast cell stabilizers
- Oral antihistamines
- Topical or nasal vasoconstrictors

Within 30 prior to Visit 1 (Screening), have altered or anticipate alteration of:

- Oral dosing of tetracycline compounds (e.g., tetracycline, doxycycline, or minocycline).
- Omega-3 or Omega-6 supplements

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

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

Within 6 months prior to Screening (Visit 1) have altered or anticipate alteration of dosing during the study:

- 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 dosing information recorded daily by the subject. The site will document this comparison along with verification of the numbers of used and unused investigational product bottles. The number 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, vehicle, or run-in product). Accountability will be ascertained by performing reconciliation between the amount of drug sent to the site and the amount unused at the time of reconciliation.

Clinical trial materials will be shipped to the investigational sites under sealed conditions. 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, vehicle, or run-in product), 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 double-masked, 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 Kala Pharmaceuticals, Inc. or designee. Randomization team members will work independently of other team members at the CRO. Study personnel, 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 posterior lid margin hyperemia
- [redacted]
- Investigator-rated assessment of conjunctival hyperemia
- Investigator-rated assessment of the character of the meibomian glands' contents
- Investigator-rated assessment of the expressibility of the meibomian glands
- TFBUT
- Corneal Fluorescein Staining
- [redacted]
- In-clinic subject-rated assessment of ocular discomfort

8. ASSESSMENT OF SAFETY

8.1. SAFETY PARAMETERS

Safety parameters include:

- Assessment of AEs
- IOP measurements
- Slit-lamp biomicroscopy
- BCVA
- Dilated ophthalmoscopy

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. RESCUE THERAPY

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).

8.5. 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, for all analyses [redacted] 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.

[redacted] Severity Assessment Score between the KPI-121 0.25% ophthalmic suspension group and the vehicle group at Visit 4 (based on the mean score for the 3 days prior to Visit 2 and Visit 4); and (2) comparison of mean posterior lid margin hyperemia [redacted] at Visit 2 between the KPI-121 0.25% ophthalmic suspension group and the vehicle group at Visit 4.

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 imputations 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. 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 will 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. Geerling G, Tauber J, Baudouin C, et al. The International Workshop on Meibomian Gland Dysfunction: Report of the subcommittee on management and treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci*. 2011;52(4):2050-2064. doi:10.1167/iovs.10-6997g.

2. 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.

3. Foulks GN, Borchman D, Yappert M, Sung-Hye K, McKay JW. Topical azithromycin therapy of meibomian gland dysfunction: Clinical response and lipid alterations. *Cornea*. 2010;29(7):781-788. doi:10.1097/ICO.0b013e3181cda38f.

4. 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.

5. 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.

6. [redacted]

7. 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.

8. 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.

16. APPENDICES

APPENDIX 1: SUMMARY OF EVENTS

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	Randomization	[redacted]	Study Visit	[redacted]	End of Study Visit
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)
Informed Consent, HIPAA Authorization and Medical History	X					
Concomitant Medication Query	X	X	X	X	X	X
Inclusion/Exclusion	X	X				
[redacted] Assessment	X					
UPT[a]	X					X
AE Assessment	X	X	X	X	X	X
Subject-Rated Ocular Discomfort Assessment	X	X	X	X	X	X
Investigator-Rated Assessment of Signs of MGD	X	X		X		X
Investigator-Rated Assessment of Bulbar Conjunctival Hyperemia	X	X		X		X
[redacted]	[redacted]	[redacted]		[redacted]		[redacted]
TFBUT	X	X		X		X
Corneal Fluorescein Staining	X	X		X		X
Unanesthetized Schirmer Test	X					
BCVA	X	X		X		X
Slit Lamp Biomicroscopy	X	X		X		X
IOP Measurement	X	X		X		X
Dilated Ophthalmoscopy	X					X
Investigational Product Administration in Clinic	X	X				
Dispense Investigational Product	X[b]	X		X		
Collect Investigational Product		X[b]		X		X

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	Randomization	[redacted]	Study Visit	[redacted]	End of Study Visit
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)
[redacted]	X	X	X	X	X	
[redacted]		X	X	X	X	X

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

APPENDIX 2: SUBJECT-RATED OCULAR DISCOMFORT ASSESSMENT

Subjects will be asked to subjectively rate their ocular discomfort severity and frequency at Visits 1-6. Site personnel will ask the subject the following question and record their answer in the eCRF.

Severity of Symptoms

On average over the past day, how would you rate the severity of your ocular discomfort (such as irritation, dryness, burning, fluctuating vision at near tasks)?

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 (such as irritation, dryness, burning, fluctuating vision at near tasks)?

0 = Never
1 = Sometimes
2 = Often
3 = Constantly

APPENDIX 3: [redacted]

Subjects will be asked to subjectively rate their ocular discomfort severity and frequency at Visit 1 for eligibility. [redacted]

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.

[redacted] SEVERITY ASSESSMENT

Please place a single line across the line below to indicate how severe, [redacted] you feel your eye discomfort (for example, irritation, dryness, burning, or fluctuating vision during reading or computer use) 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, irritation, dryness, burning, or fluctuating vision during reading or computer use) was:

[redacted] _____ [redacted]

APPENDIX 4: INVESTIGATOR-RATED ASSESSMENT OF SIGNS OF MGD

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; vessels 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 (10 glands in the middle part of lower lid)

0 =	Normal	Clear liquid
1 =	Mild	Hazy, turbid liquid
2 =	Moderate	Turbid liquid with clumps
3 =	Severe	Solid (paste)
4 =	No glands expressible	

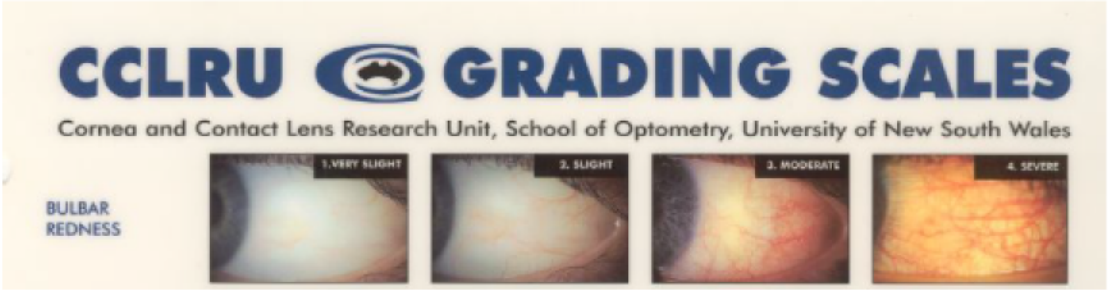
The most severe finding in any one meibomian gland should be recorded for this evaluation

Expressibility of Meibomian Gland (10 glands in the middle part of lower lid)

0 =	Normal	9 – 10 glands expressible
1 =	Mild	6 – 8 glands expressible
2 =	Moderate	3 – 5 glands expressible
3 =	Severe	1 – 2 glands expressible
4 =	No glands expressible	

APPENDIX 5: INVESTIGATOR-RATED ASSESSMENT OF BULBAR CONJUNCTIVAL HYPEREMIA

Investigators will rate bulbar conjunctival hyperemia at Visits 1, 2, 4, and 6 using the Cornea and Contact Lens Research Unit (CCLRU).



0 = None
1 = Very Slight
2 = Slight
3 = Moderate
4 = Severe

Appendix 6: Unanesthetized Schirmer Test

Unanesthetized Schirmer Test will be conducted at Visit 1.
Identical Schirmer Test strips will be supplied to each site.

Unanesthetized Schirmer Test

- While still in the plastic sheath, fold the notched end of the unanesthetized Schirmer Test 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 of the ETDRS chart is visible.
- Instruct the subject to relax and look at the chart while blinking normally or have patients gently close eyes.
- Remove strips 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.

APPENDIX 7: ETDRS BEST CORRECT 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; the subject should be encouraged 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 throughout the 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 8: 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 width and intensity that provide optimal evaluation of the 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

Edema
0 = Normal, no swelling of the lid tissue
1 = Abnormal

Conjunctiva

Edema
0 = Normal, no swelling of the conjunctiva
1 = Abnormal

Palpebral Conjunctival Erythema
0 = Normal, no redness 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 9: CORNEAL FLUORESCEIN STAINING

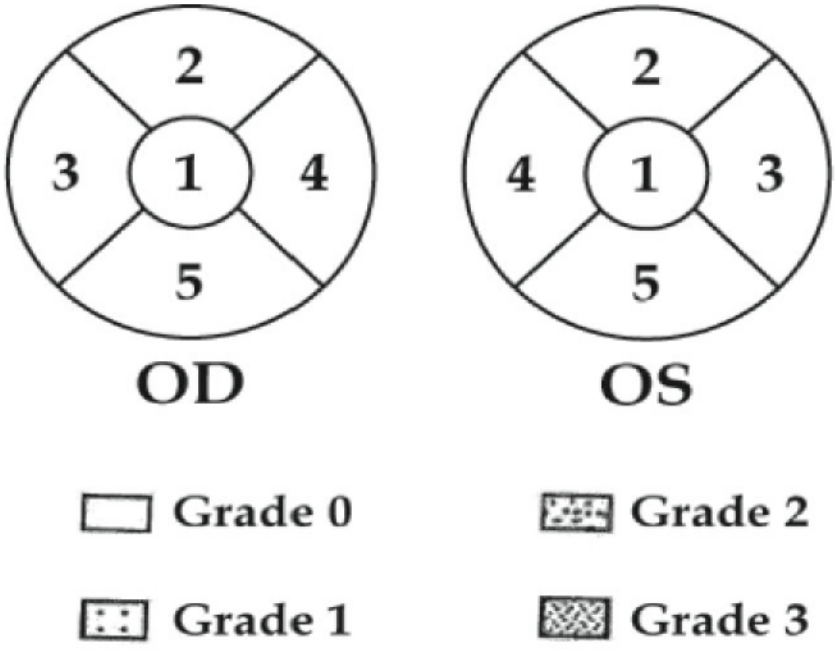
Corneal staining will be performed at Visit 1, 2, 4, and 6. Corneal staining assessment will be performed using methods developed by the National Eye Institutes (NEI) Dry Eye Workshop[7,8].

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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1
3
5
OS
Grade 0
Grade 2
Grade 1
Grade 3

APPENDIX 10: IOP MEASUREMENT

IOP measurements will be performed utilizing Goldmann applanation tonometery according to the Investigator's standard procedure. All pressures 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 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]

[redacted]

APPENDIX 14: TEAR FILM BREAK-UP TIME

This assessment should be performed by both the investigator and an individual to record times.

- Perform the examination with the slit lamp at 16X magnification and cobalt blue illumination.
- Draw 5 µL of 2% sodium fluorescein into the supplied 2-20 µl micropipette fitted with a clean pipette tip.
- Carefully press the plunger of the pipette, allowing a drop to form on the end of the tip.
- Gently touch the drop at the tip to the lower palpebral conjunctiva of the right eye.
- In order to thoroughly mix the fluorescein with the tear film, ask the subject to blink three full times for even distribution.
- Instruct the subject to hold his or her eye open for as long as possible.
- Scan the cornea, focusing on the tear film and epithelium. Do not hold the light steady in one position. Using a stopwatch, measure the time interval between a complete blink and the appearance of the first black or dry eye area.
- Perform this assessment three times in the right eye, recording each time in the case report form.
- Repeat these steps for the left eye.