NCT02793817

Study ID:
KPI-121-C-005

Study Title:
A Phase 3, Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Efficacy of KPI-121 1.0% Ophthalmic Suspension in Subjects with Postsurgical Inflammation and Pain

Date:
24 Feb 2017

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-005

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Sponsor:	Kala Pharmaceuticals, Inc. 100 Beaver St, Suite 201 Waltham, MA 02453
Medical Monitor:	[redacted]
Issue Date:	Original: 03 Feb 2016 Amendment 01: 03 May 2016 Amendment 02: 13 Jul 2016 Amendment 03: 23 Aug 2016 Amendment 04: 31 Jan 2017 Amendment 05: 24 Feb 2017
Approved:	24 February 2017

[redacted]

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-005
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-005: A Phase 3, Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Efficacy of KPI-121 1.0% Ophthalmic Suspension in Subjects with Postsurgical Inflammation and Pain
Objectives:	The primary objective of the study is to investigate the efficacy and safety of KPI-121 1.0% ophthalmic suspension compared to placebo in subjects who have undergone cataract surgery.
Study Population:	The study population will consist of subjects who have undergone routine uncomplicated cataract surgery and experience ocular inflammation postoperatively.
Number of Subjects:	Approximately 720 subjects who are candidates for cataract surgery will be screened. One study eye from approximately 500 subjects will be randomized.
Investigational Products:	KPI-121 1.0% ophthalmic suspension or placebo will be supplied as investigational product.
Route and Duration of Administration:	1 to 2 drops of investigational product will be instilled in the study eye two times per day (BID) for 14 ± 1 days.
Study Design:	This is a Phase 3, multicenter, double-masked, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of KPI-121 1.0% ophthalmic suspension versus placebo in subjects who require treatment of postoperative anterior ocular inflammation. Approximately 720 subjects who are candidates for cataract surgery will be screened and approximately 500 subjects who, after undergoing routine, uncomplicated cataract surgery, present at Visit 3 (Day 1) with ≥ 2 anterior chamber cells in the study eye will be randomized in this study at approximately 35 centers located in the United States (US). Subjects who experience postoperative inflammation on the first day following routine, uncomplicated, cataract surgery and who meet all other eligibility criteria will be randomized to one of two study groups in an approximate 1:1 ratio to KPI-121 1.0% ophthalmic suspension dosed BID or placebo dosed BID. Investigational product or placebo will be initiated on the day following surgery and instilled as one to two drops in the study eye BID for 14 ± 1 days.

	This study will include up to 7 clinic visits (including the surgery day) over 18 to 33 days total study duration. Visit 1 (Screening) will occur between 14 to 1 day(s) prior to surgery, and subjects who meet preoperative screening inclusion/exclusion criteria will be entered into the study. At Visit 2 (Surgery/Day 0) subjects will undergo routine cataract surgery according to the Investigator's normal procedures. Visit 3 (Randomization/Day 1) will occur on the day following surgery. Subjects who meet the qualifying postoperative randomization criteria will be eligible for randomization to one of the two study groups and will initiate investigational product on that day. Following randomization, subjects will be instructed to return to the clinic to be evaluated at Visit 4 (Day 4 ± 1 day), Visit 5 (Day 8 ± 1 day), and Visit 6 (Day 15 ± 1 day). The last dose of investigational product will be administered upon completion of 14 days of evaluation. Following the End of Investigational Product Use Visit (Visit 6; Day 15 ± 1 day), subjects will be asked to return to the clinic on Day 18 ± 1 day for Visit 7 (Follow-Up) and will be released from the study.
	
	Assessments in this study will include:
	
	• Subject-Rated Ocular Pain assessment
	• Snellen Distance Visual Acuity (VA) by Pinhole Method
	• Slit Lamp Biomicroscopy:
	  o Signs of anterior ocular inflammation (cell and flare grading)
	  o Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
	• Intraocular Pressure (IOP) Measurement
	• Dilated Ophthalmoscopy
	• Rescue Therapy Assessment
	• Concomitant Medication Use Assessment
	• Assessments of Adverse Events (AEs)

Efficacy Endpoint	**Primary Efficacy Endpoints:** The primary endpoints of this study will be evaluated using hierarchical statistical testing in the following sequence: 1. Proportion of study eyes with complete resolution of anterior

	chamber cells (grade = 0) at Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. 2. Proportion of study eyes with complete resolution of ocular pain (grade = 0) at Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. **Secondary Efficacy Endpoints:** 1. Proportion of study eyes with complete resolution of ocular pain (grade = 0) at Visit 4 (Day 4 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. This endpoint will be tested at $\alpha = 0.0167$. 2. Proportion of study eyes with complete resolution of anterior chamber flare (grade = 0) at Visit 4 (Day 4 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. This endpoint will be tested at $\alpha = 0.0167$. 3. Change from baseline in mean anterior chamber cell count at Visit 4 (Day 4 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. This endpoint will be tested at $\alpha = 0.0167$.
Safety Endpoints	Assessment of AEs Snellen Distance VA by Pinhole Method Slit Lamp Biomicroscopy IOP measurement Dilated Ophthalmoscopy Change from baseline to each post-surgery visit in ocular signs: • Palpebral conjunctival erythema • Corneal edema • Hyphema • Ciliary flush

	• Bulbar conjunctival injection
Eligibility Criteria:	**Inclusion Criteria:** At Visit 1, 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. 4. Are candidates for routine, uncomplicated cataract surgery [e.g., phacoemulsification with posterior chamber intraocular lens (IOL) implantation, not combined with any other surgery]. 5. In the Investigator's opinion, have potential postoperative Snellen Distance VA by pinhole method of at least 20/200 in the study eye. 6. 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 three 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 three 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 three 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 six 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.

7. Are postmenopausal women who have had no menstrual cycle for at least one year prior to Visit 1 or are women who 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 they may not:

1. Require concurrent ocular therapy (either eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, antihistamines, or decongestants within 2 days prior to surgery and for the duration of the study.
2. Require treatment with systemic NSAIDs, with the exception of ≤ 81 mg/day of acetylsalicylic acid (ASA or aspirin), within 2 days prior to surgery and for the duration of the study.

	3. Require treatment with systemic (except stable maintenance dose of inhaled or intranasal corticosteroids) or ocular (either eye) corticosteroids (other than investigational product) within 14 days prior to cataract surgery and for the duration of the study. 4. Require concurrent systemic or ocular therapy with immunosuppressants (with the exception of oral corticosteroids less than prednisone 11 mg/day or equivalent) within 30 days prior to surgery and for the duration of the study. 5. Require change in treatment with anticholinergics or oral corticosteroids (dose must be less than prednisone 11 mg/day or equivalent) within six months prior to Visit 1. 6. Require change in stable treatment with antidepressants within 6 months prior to Visit 1. 7. Require change in use of nutraceuticals or multivitamins during trial participation. 8. Have known hypersensitivity or contraindication to the investigational product(s) or their components. 9. Use any topical ophthalmic medications including glaucoma medications, all eye drops (except antibiotic eye drops considered to be included in post cataract surgery standard of care treatment), all gels or artificial tears within 2 days prior to surgery and for the duration of the study. Note: Besifloxacin Ophthalmic Suspension is not permitted within 2 days prior to surgery or for the duration of the study. 10. Use any topical eyelash growth medications within 7 days prior to surgery and for the duration of the study. 11. Have history of glaucoma, IOP >21 mmHg at the screening or randomization visit(s), or are being treated for glaucoma in either eye. 12. Wear contact lenses for 4 weeks prior to Visit 1 and throughout the study. 13. Be monocular or have Snellen Distance VA by pinhole method of 20/200 or worse in the non-study eye. 14. Have had penetrating intraocular surgery in the study eye within 3 months or within two weeks in the fellow eye. 15. Have had corneal refractive surgery or corneal transplantation (full thickness, anterior, or posterior) within the past year or are unstable and/or require medication. 16. Have a diagnosis of:

	a. Ongoing ocular infection. b. Severe/serious ocular condition that in the judgment of the Investigator could confound study assessments or limit compliance. c. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance. 17. Have been exposed to an investigational drug within 30 days prior to screening or up to 18 days following surgery. 18. 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. 19. Have a known history of alcohol and/or drug abuse. 20. 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. **Randomization Criteria:** **To qualify for randomization at Visit 3 (Postoperative Day 1)**, a subject must: 1. Have undergone routine, uncomplicated cataract surgery (e.g., phacoemulsification with posterior chamber IOL implantation, not combined with any other surgery). 2. Have ≥ Grade 2 anterior chamber cells. 3. Continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions (Sections 4.1 and 4.2), and must not have taken prohibited medications (Section 6.2.2).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ASA	Acetylsalicylic Acid
BID	Twice Daily
°C	Degrees Celsius
CME	Cystoid Macular Edema
CRF	Case Report Form
CRO	Contract Research Organization
EE	Efficacy Evaluable
eCRF	Electronic Case Report Form
°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
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
KPI	Kala Pharmaceuticals, Inc.
LE	Loteprednol etabonate
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of Mercury
MAR	Missing at random
MPP	Mucus Penetrating Particles
NDA	New Drug Application
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OTC	Over the Counter
PDF	Portable Document Format
pH	Potential Hydrogen
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SLT	Selected Laser Trabeculoplasty
TNF	Tumor Necrosis Factor

UPT	Urine Pregnancy Test
US	United States of America
VA	Visual Acuity
WOCBP	Women of Child Bearing Potential
w/v	Weight to Volume

1. INTRODUCTION

Intraocular inflammation is an anticipated sequela of intraocular surgery such as cataract removal and intraocular lens (IOL) placement. In general, trauma to the internal structures of the eye is accompanied by the production of prostaglandins and other vasoactive moieties, an increase in blood flow to the affected area, and extravasations of protein and cellular blood elements. Postoperative inflammation is manifested principally as bulbar erythema, corneal edema, ciliary flush and aqueous cells and flare.

If left untreated, inflammation generally resolves within 2 to 4 weeks after surgery; however 20% to 80% of patients present with anterior chamber cells and/or flare 2 weeks after cataract surgery and IOL placement. Since untreated intraocular inflammation following cataract surgery may lead to complications such as cystoid macular edema (CME) (Apple et al., 1992; Tennant, 1978), treatment with anti-inflammatory agents such as glucocorticosteroids is employed to reduce pain and discomfort, and to facilitate recovery of the blood-aqueous barrier. When administered at the time of surgery and during the immediate postoperative period, glucocorticosteroids can reverse the clinical and non-clinical manifestations of inflammation (Leopold, 1985). In the United States (US), topical glucocorticosteroids are routinely prescribed for at least 2 weeks following cataract surgery, with longer treatment prescribed in cases of severe or unremitting inflammation.

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. Loteprednol etabonate was approved by Food and Drug Administration (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 postoperative ocular inflammation. Despite its attractive pharmacologic activity, wherein the drug is active at the site of administration but is rapidly metabolized to an inactive compound following absorption, Lotemax requires frequent dosing (four times per day) which may reduce patient compliance.

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

pharmacokinetic profile has the potential to reduce either dosing strength or frequency of loteprednol etabonate as compared to Lotemax.

Kala Pharmaceuticals, Inc. intends to develop KPI-121 for the treatment of postoperative inflammation and pain following ocular surgery.

1.1. DESCRIPTION OF INVESTIGATIONAL PRODUCT

KPI-121 contains submicron particles of loteprednol etabonate suspended in a formulation consisting of excipients that have been used in other FDA-approved ophthalmic products. Kala is developing this improved loteprednol etabonate formulation for the treatment of postoperative anterior segment inflammation and pain.

KPI-121 is a sterile, aqueous submicron suspension of loteprednol etabonate and will be filled in a white, low-density polyethylene plastic bottle with a translucent, controlled-drop polypropylene tip, a pink polypropylene cap and a white polyethylene tamper-evident overcap. The bottle will be a 5 mL dropper bottle with a nominal fill of 3.2 mL.

For this trial, KPI-121 investigational product will be supplied as 1.0% ophthalmic suspension. Each mL of KPI-121 1.0% ophthalmic suspension contains 10 mg loteprednol etabonate as the active ingredient. Inactive ingredients in KPI-121 investigational product are [redacted] as preservative. KPI-121 1.0% ophthalmic suspension is essentially isotonic and is buffered to maintain a power of hydrogen (pH) of 5.0 – 7.0.

The placebo control has the same excipient composition as KPI-121 1.0% ophthalmic suspension but does not contain loteprednol etabonate. The placebo control contains [redacted] as preservative. The placebo control is essentially isotonic and buffered to maintain pH 5.0 – 7.0. It is a sterile, aqueous solution supplied in the same white, low-density polyethylene plastic bottle with the same translucent, controlled-drop polypropylene tip, pink polypropylene cap and white polyethylene tamper-evident overcap as KPI-121 1% ophthalmic suspension investigational product.

1.2. JUSTIFICATION FOR ROUTE OF ADMINISTRATION AND DOSE SELECTION

KPI-121 1.0% will be administered as a topical ophthalmic suspension.

Subjects are expected to self-administer one to two drops of either KPI-121 1.0% ophthalmic suspension or placebo control BID.

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 effect and tolerability for 14 days of KPI-121 1.0% ophthalmic suspension dosed BID.

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

Approximately 720 subjects who are candidates for cataract surgery will be screened. One study eye from approximately 500 subjects who have undergone routine, uncomplicated cataract surgery and have ≥ 2 anterior chamber cells in the study eye at Visit 3 (Day 1) will be evaluated at approximately 35 centers located in the US.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. OBJECTIVE

The primary objective of this study is to investigate the safety and efficacy of KPI-121 1.0% ophthalmic suspension compared to placebo in subjects who have undergone cataract surgery.

3. TRIAL DESIGN

3.1. PRIMARY EFFICACY ENDPOINTS

The primary endpoints of this study will be evaluated using hierarchical statistical testing in the following sequence:

1. Proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID.

2. Proportion of study eyes with complete resolution of pain (grade = 0) at Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID.

3.2. SECONDARY EFFICACY ENDPOINTS

1. Proportion of study eyes with complete resolution of ocular pain (grade = 0) at Visit 4 (Day 4 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. This endpoint will be tested at $\alpha = 0.0167$.
2. Proportion of study eyes with complete resolution of anterior chamber flare (grade = 0) at Visit 4 (Day 4 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. This endpoint will be tested at $\alpha = 0.0167$.
3. Change from baseline in mean anterior chamber cell count at Visit 4 (Day 4 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID. This endpoint will be tested at $\alpha = 0.0167$.

3.3. SAFETY ENDPOINTS

- Assessment of AEs
- Snellen Distance VA by pinhole method
- Slit Lamp Biomicroscopy
- IOP Measurement
- Dilated Ophthalmoscopy
- Change from baseline to each post-surgery visit in ocular signs:

- Palpebral conjunctival erythema
- Corneal edema
- Hyphema
- Ciliary flush
- Bulbar conjunctival injection

3.4. DESCRIPTION OF TRIAL DESIGN

This is a Phase 3, multicenter, double-masked, randomized, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of KPI-121 1.0% ophthalmic suspension versus placebo in subjects who require treatment of postoperative anterior ocular inflammation. Approximately 720 subjects who are candidates for cataract surgery will be screened and approximately 500 subjects who, after undergoing routine, uncomplicated cataract surgery, present at Visit 3 (Day 1) with ≥ 2 anterior chamber cells in the study eye will be randomized in this study at approximately 35 centers located in the US.

Subjects who experience postoperative inflammation on the first day following routine, uncomplicated, cataract surgery and who meet all other eligibility criteria will be randomized to one of two study groups in an approximate 1:1 ratio:

- KPI-121 1.0% ophthalmic suspension, BID
- Placebo, BID

Dosing of investigational product will be initiated on the day following surgery, instilled as 1-2 drops in the study eye BID for 14 ± 1 days. The first dose of investigational product will be administered by the subject under the supervision of a designated study team member who is otherwise uninvolved in the assessment or evaluation of the subject. Except for this investigational product administration, no other information or discussion regarding the subject's assigned investigational product will be exchanged, in order to maintain the masking for this trial.

This study will include up to 7 clinic visits (including the surgery day) over 18 to 33 days total study duration. Visit 1 (Screening) will occur between 14 to 1 day(s) prior to surgery and subjects who meet preoperative screening inclusion/exclusion criteria will be entered into the study. At Visit 2 (Surgery/Day 0), subjects will undergo routine cataract surgery according to the Investigator's normal procedures. Visit 3 (Randomization/Day 1) will occur on the day following surgery. Subjects who meet the qualifying postoperative randomization criteria will be eligible for randomization to one of the two study groups and will initiate dosing with investigational product on that day. Following randomization, subjects will be instructed to instill investigational product in the study eye two times a day (BID) for 14 ± 1 days, up until

Visit 6, and return to the clinic to be evaluated at Visit 4 (Day 4 ± 1 day), Visit 5 (Day 8 ± 1 day), and Visit 6 (Day 15 ± 1 day/ End of Investigational Product Use Visit). Subjects will be asked to return to the clinic for Visit 7 (Day 18 ± 1 day) for follow-up and then will be released from the study.

A summary of events is provided in Appendix 1. Procedures and assessments in this study will include:

- Routine uncomplicated cataract surgery
- Subject-Rated Ocular Pain Assessment (Appendix 2)
- Snellen Distance VA by Pinhole Method (Appendix 3)
- Slit Lamp Biomicroscopy (Appendix 4):
  - Signs of anterior ocular inflammation (cell and flare grading)
  - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
- IOP Measurement (Appendix 5)
- Dilated Ophthalmoscopy (Appendix 6)
- Rescue Therapy Assessment
- Concomitant Medication Use Assessment
- Dosing Compliance Assessment
- Assessments of AEs

A study schematic follows (Figure 1).

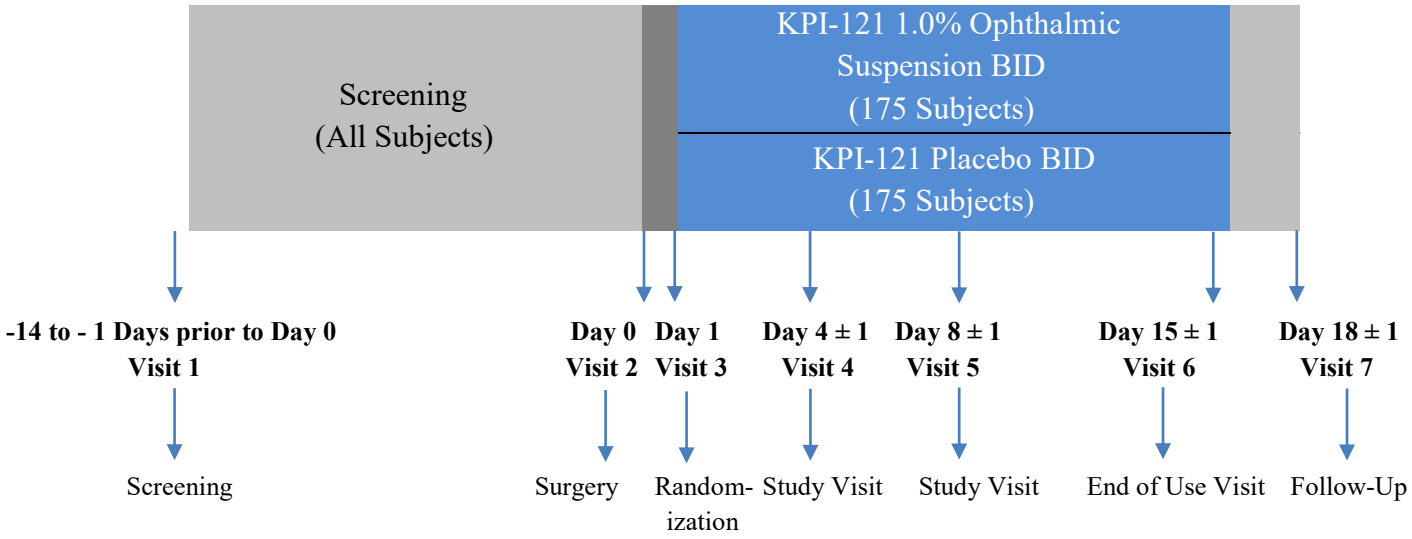

FIGURE 1: STUDY SCHEMATIC

3.4.1. Investigational Product

KPI-121 1.0% w/v will be supplied as a suspension in opaque dropper bottles. KPI-121 1.0% ophthalmic suspension is a sterile, aqueous, submicron suspension of LE and will be supplied in a 5 mL, white, low-density polyethylene plastic dropper bottle with a translucent,

controlled-drop polypropylene tip, a pink polypropylene cap and a white polyethylene tamper-evident overcap. Each bottle contains 3.2 mL (nominal fill) of investigational product.

Subjects randomized to the placebo control arm will receive the same bottles containing all components at the concentrations used in the KPI-121 1.0% 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 1: COMPOSITION OF KPI-121 1.0% (W/V) INVESTIGATIONAL PRODUCT

Ingredient	Function	Concentration (% w/v)
Loteprednol etabonate	Active pharmaceutical ingredient	1.0
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

TABLE 2: COMPOSITION OF PLACEBO

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

The randomized investigational product kit consists of a box with two dropper bottles of investigational product. At Visit 3, eligible subjects will receive one bottle of investigational product. The second bottle will be retained at the site and provided to the subject in the event

the subject needs additional investigational product during the treatment period. Both the box label and dropper bottle labels will contain the following information: sponsor name, protocol and randomization number, storage temperature and required statement(s) per the appropriate regulatory agency.

The investigational product will be stored in a secure area with limited access at 15-25°C/59 - 77°F with upper limit excursions to 30°C /86°F allowed. Subjects will be instructed to shake the investigational product bottle prior to administering each dose. On days when subjects receive the first dose in the clinic (Visit 3), the in-clinic dose will count as one of their two (BID) daily doses. Subjects will then self-administer an additional dose of investigational product later that day. Visit 3 should be scheduled in the morning to allow subjects to receive a full day of BID dosing.

On all other study evaluation days, subjects will be asked to instill one "Morning Dose" and one "Evening Dose" approximately 12 hours following the previous dose.

3.4.2. Methods to Minimize Bias

To minimize bias, the following measures will be taken:

- Investigational product assignment (KPI-121 1.0% ophthalmic suspension versus placebo) 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, 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.
4. Are candidates for routine, uncomplicated cataract surgery (e.g., phacoemulsification with posterior chamber IOL implantation, not combined with any other surgery).
5. In the Investigator's opinion, have potential postoperative Snellen Distance VA by pinhole method of at least 20/200 in the study eye.
6. Are WOCBP who are not pregnant or lactating and not sexually active (i.e., abstinent) for 14 days prior to Visit 1 and willing to remain so through 30 days following Visit 6 or the last administration of the investigational product or until completion of the subject's first menstrual cycle following the last administration of the investigational product, whichever period of time is longer. Alternatively, WOCBP who are not abstinent must have been using one of the following acceptable methods of birth control for the times specified:
   a. IUD in place for at least three 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 three 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 three 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 at least six 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.

7. Are postmenopausal women who have had no menstrual cycle for at least one year prior to Visit 1 or are women who 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 they may not:

1. Require concurrent ocular therapy (either eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, antihistamines, or decongestants within 2 days prior to surgery and for the duration of the study.
2. Require treatment with systemic NSAIDs, with the exception of ≤ 81 mg/day of acetylsalicylic acid (ASA or aspirin), within 2 days prior to surgery and for the duration of the study.
3. Require treatment with systemic (except stable maintenance dose of inhaled or intranasal corticosteroids) or ocular (either eye) corticosteroids (other than investigational product) within 14 days prior to cataract surgery and for the duration of the study.
4. Require concurrent systemic or ocular therapy with immunosuppressants (with the exception of oral corticosteroids less than prednisone 11 mg/day or equivalent) within 30 days prior to surgery and for the duration of the study.
5. Require change in treatment with anticholinergics or oral corticosteroids (dose must be less than prednisone 11 mg/day or equivalent) within six months prior to Visit 1.
6. Require change in stable treatment with antidepressants within 6 months prior to Visit 1.
7. Require change in use of nutraceuticals or multivitamins during trial participation.

8. Have known hypersensitivity or contraindication to the investigational product(s) or their components.
9. Use any topical ophthalmic medications including glaucoma medications, all eye drops (except antibiotic eye drops considered to be included in post cataract surgery standard of care treatment), all gels or artificial tears within 2 days prior to surgery and for the duration of the study.
   NOTE: Besifloxacin Ophthalmic Suspension is not permitted within 2 days prior to surgery or for the duration of the study.
10. Use any topical eyelash growth medications within 7 days prior to surgery and for the duration of the study.
11. Have history of glaucoma, IOP >21 mmHg at the screening or randomization visit(s), or are being treated for glaucoma in either eye.
12. Wear contact lenses for 4 weeks prior to Visit 1 and throughout the study.
13. Be monocular or have Snellen Distance VA by pinhole method of 20/200 or worse in the non-study eye.
14. Have had penetrating intraocular surgery in the study eye within 3 months or within two weeks in the fellow eye.
15. Have had corneal refractive surgery or corneal transplantation (full thickness, anterior, or posterior) within the past year or are unstable and/or require medication.
16. Have a diagnosis of:
    a. Ongoing ocular infection.
    b. Severe/serious ocular condition that in the judgment of the Investigator could confound study assessments or limit compliance.
    c. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance.
17. Have been exposed to an investigational drug within 30 days prior to screening or up to 18 days following surgery.
18. 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.
19. Have a known history of alcohol and/or drug abuse.
20. 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.

4.3. RANDOMIZATION CRITERIA

To qualify for randomization at Visit 3 (Postoperative Day 1), a subject must:

1. Have undergone routine, uncomplicated cataract surgery (e.g., phacoemulsification with posterior chamber IOL implantation, not combined with any other surgery).
2. Have ≥ Grade 2 anterior chamber cells.
3. Continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions (Section 4.1 and Section 4.2), and must not have taken prohibited medications (Section 6.2.2).

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: Screening Visit (Day -14 to Day -1)

The screening visit will occur no more than 14 days and no less than one (1) day prior to Visit 2/Surgery. After obtaining written informed consent and HIPAA authorization, site staff will perform/assess the following in the order suggested below:

- Assign each subject screened a Subject Identification (ID) consisting of a three-digit Investigator number plus a three-digit number starting with number 501. The Subject ID will be used as the primary subject identifier for the duration of the study.
- Perform the following assessments/collect the following information (**NOTE:** All ocular assessments must be performed in both eyes):
  - Non-ocular and ocular medical history
  - Concomitant medication usage and medications taken during the 30 days prior to screening will be captured in the case report form (CRF)
  - Inclusion/exclusion criteria
  - Urine pregnancy test (UPT) for women of childbearing potential
  - Snellen Distance VA by pinhole method
  - Slit Lamp Biomicroscopy:
    - Signs of anterior ocular inflammation (cell and flare grading)
    - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
  - IOP Measurement
  - Dilated Ophthalmoscopy
- Schedule subjects to return for surgery (Visit 2) in no more than 14 ± 1 day.

5.1.2. Visit 2: Surgery Visit (Day 0)

Pre-surgical Procedures:

This visit will occur no more than 15 days and no less than 1 day after Visit 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
- Routine pre-surgical care and procedures as determined by the Investigator

Surgical Procedure

The surgeon will perform his or her routine cataract surgical procedure. The surgeon's usual pre-operative sterile scrub and draping procedures should be performed.

Post-Surgical Procedures

- Assess the occurrence of any AEs.
  NOTE: Changes that are expected due to uncomplicated cataract surgery will not be classified as AEs.
- Provide instructions regarding routine post-surgical care and instructions.
- Medications routinely administered prior to and following cataract surgery will be collected in the source documents. These medications will be indicated for routine cataract surgery and are not expected to be associated with treatment for AEs unless otherwise indicated.
- Schedule the subject to return to the clinic on the following day (Day 1) for Visit 3.

5.1.3. Visit 3: Randomization Visit (Day 1)

The randomization visit will occur 1 day after Visit 2/Surgery Visit. This visit should be scheduled in the morning (if possible) to allow for administration of two doses of investigational product during the day for eligible subjects.

Eligible subjects who meet the randomization criteria (Section 4.3) will continue in the study.

The following will be performed/assessed (**NOTE:** All ocular assessments must be performed in both eyes):

- Obtain Subject-Rated Ocular Pain Assessment
- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit (**NOTE**: Expected changes or the presence of inflammation resulting from routine uncomplicated cataract surgery will not be captured as AEs.)
- Perform:
  - Snellen Distance VA by pinhole method
  - Slit Lamp Biomicroscopy

        - Signs of anterior ocular inflammation (cell and flare grading)
        - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
    - IOP Measurement

Upon verification of study eligibility (Section 4.3), eligible subjects will be randomized to receive either KPI-121 1.0% ophthalmic suspension dosed BID or placebo dosed BID. The following will be performed for all randomized subjects:

- Administer the first dose of double-masked investigational product in the clinic under the supervision of designated study personnel.
- Prior to administration of investigational product, remind the subjects regarding the proper method for instillation including but not limited to shaking investigational product bottle prior to each instillation.
- Since subjects will receive one dose of investigational product in the clinic, instruct the subject to self-administer one additional dose of investigational product on the first day.
- Assess the occurrence of any AEs after investigational product administration
- Dispense investigational product kits and instructions for administration
- Schedule subjects to return for Visit 4 on Day 4 ± 1 day.

5.1.4. Visit 4: Study Visit (Day 4 ± 1 day)

This visit will occur on Day 4 ± 1 day and the following evaluations will be performed/assessed (**NOTE:** All ocular assessments must be performed in both eyes.):

- Obtain Subject-Rated Ocular Pain Assessment
- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Perform:
    - Snellen Distance VA by pinhole method
    - Slit Lamp Biomicroscopy
        - Signs of anterior ocular inflammation (cell and flare grading)
        - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
    - IOP Measurement
- Review dosing compliance. If needed, the second bottle of investigational product will be dispensed to the subject.
- Instruct subjects to continue investigational product and return for Visit 5 on Day 8 ± 1 day.

5.1.5. Visit 5: Study Visit (Day 8 ± 1 day)

This visit will occur on Day 8 ± 1 day and the following evaluations will be performed/assessed (**NOTE:** All ocular assessments must be performed in both eyes):

- Obtain Subject-Rated Ocular Pain Assessment
- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Perform:
  - Snellen Distance VA by pinhole method
  - Slit Lamp Biomicroscopy
    - Signs of anterior ocular inflammation (cell and flare grading)
    - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
  - IOP Measurement
- Review dosing compliance. If needed, the second bottle of investigational product will be dispensed to the subject.
- Instruct subjects to continue investigational product and return for Visit 6 on Day 15 ± 1 day.

5.1.6. Visit 6: End of Investigational Product Use (Day 15 ± 1 day)

The end of investigational product use visit will occur on Day 15 ± 1 day and the following will be performed/assessed (**NOTE:** All ocular assessments must be performed in both eyes.):

- Obtain Subject-Rated Ocular Pain Assessment
- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Collect of used and unused investigational product
- Perform:
  - UPT
  - Snellen Distance VA by pinhole method
  - Slit Lamp Biomicroscopy
    - Signs of anterior ocular inflammation (cell and flare grading)
    - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
  - IOP Measurement
  - Dilated Ophthalmoscopy
- Review dosing compliance.

At the end of Visit 6, subjects with inflammation that has not resolved will be treated according to the Investigator's discretion. Regardless of treatment and after cessation of experimental medication, all subjects will be asked to return for follow-up on Days 18 ± 1 day for Visit 7.

5.1.7. Visit 7: Follow-Up Visit (Days 18 ± 1 day)

This follow-up visit will occur on Day 18 ± 1 day and the following will be performed/assessed (**NOTE:** All ocular assessments must be performed in both eyes.):

- Obtain Subject-Rated Ocular Pain Assessment
- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Perform:
  - Snellen Distance VA by pinhole method
  - Slit Lamp Biomicroscopy
    - Signs of anterior ocular inflammation (cell and flare grading)
    - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
  - IOP Measurement

5.1.8. Early Termination Visit

In the event of termination prior to Visit 6 but following Visit 3, every attempt will be made to ensure that the following will be performed/assessed (**NOTE:** All ocular assessments must be performed in both eyes.):

- Obtain Subject-Rated Ocular Pain Assessment
- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Collect of used and unused investigational product and assessment of compliance via the daily dosing information recorded by the subject.
- Perform:
  - UPT
  - Snellen Distance VA by pinhole method
  - Slit Lamp Biomicroscopy
    - Signs of anterior ocular inflammation (cell and flare grading)
    - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection

- IOP Measurement
- Dilated Ophthalmoscopy

5.2. 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.

5.3. 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 electronically entered from the source documentation into the eCRF. After study completion, an archival copy [e.g., portable document format (PDF)] of the eCRF data will be retained by the site.

5.3.1. 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.

5.4. 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 7.

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.

6. TREATMENT OF SUBJECTS

6.1. INVESTIGATIONAL PRODUCTS TO BE ADMINISTERED

KPI-121 1.0% ophthalmic suspension or placebo solution will be supplied as study product. One kit of randomized study product containing two dropper bottles will be allocated to each subject at Visit 3. Only one bottle will be dispensed to the subject at Visit 3. The second bottle will be retained at the site and provided to the subject if needed during the treatment period. The study product will be stored at the site in a secure area with limited access at 15-25°C/59-77°F with upper limit excursions to 30°C /86°F allowed.

Subjects will be asked to administer study product twice each day. Prior to each instillation of study product, subject will be instructed to shake the study product bottle. The subjects will record daily the time of administration of each dose of study product in the Dosing Diary (Appendix 7).

Compliance with instillation of study product will be reviewed and assessed at each clinic visit.

6.2. CONCOMITANT MEDICATIONS

With the exception of pre- and post-operative standard of care medications, all medication that the subject has taken 30 days prior to Visit 1 and through Visit 7 or discontinuation from the study will be recorded in the eCRF and the subject chart. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, indication, and whether or not the medication was taken due to an AE will be recorded for each medication.

6.2.1. Permitted Medications

Medications not specifically excluded in Section 6.2.2 may be taken as necessary. Concomitant treatment with antibiotics at the discretion of the Investigator is allowed (with the exception of besifloxacin). Medications routinely administered and not explicitly prohibited in this protocol used as part of an uncomplicated cataract surgery procedure are allowed. These medications will be collected in the source documentation and are not captured within the eCRF unless there is a change to the standard of care as documented in the source document. Further, the routine medications administered as part of routine cataract surgery are not expected to be associated with treatment for AEs unless otherwise indicated. Note: Any medication administered as part of the routine surgery that is ongoing subsequent to the surgical procedure, should be captured in the eCRF as a concomitant medication.

6.2.2. Medications Not Permitted

Use of the following medications is not allowed during the study and for the timeframes specified:

Within 2 days prior to surgery (Visit 2) and for the duration of the study:

- Ocular NSAIDs
- Systemic NSAIDs with the exception of ≤81 mg/day of acetylsalicylic acid (ASA or aspirin)
- Ocular mast cell stabilizers
- Ocular antihistamines
- Ocular decongestants
- All eye drops (except antibiotic eye drops considered to be included in post cataract surgery standard of care treatment). Note: Besifloxacin Ophthalmic Suspension is not permitted within 2 days prior to the surgery or for the duration of the study.
- Glaucoma medications
- All topical ophthalmic gels or artificial tears

Within 7 days prior to surgery (Visit 2) and for the duration of the study:

- Topical eyelash growth medications

Within 14 days prior to surgery (Visit 2) and for the duration of the study:

- Systemic or ocular corticosteroids other than study product (except stable maintenance dose of inhaled or intranasal corticosteroids)

Within 30 days prior to surgery (Visit 2) and for the duration of the study:

- Ocular immunosuppressants (e.g., Restasis®)
- Systemic immunosuppressants (with the exception of oral corticosteroids less than prednisone 11 mg/day or equivalent)
- Other investigational products

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

- Anticholinergics
- Antidepressants

- Oral corticosteroids (dose must be less than prednisone 11 mg/day or equivalent)

NOTE: Dose must remain stable throughout the course of the study

If using nutraceuticals or multivitamins, subjects may not alter their stable dose throughout the study.

6.3. STUDY PRODUCT USE COMPLIANCE

Compliance will be assessed by comparing study 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 study product bottles. The numbers of missed doses as assessed at each clinic visit should be documented in the eCRF.

6.4. DRUG ACCOUNTABILITY

Sponsor study monitors or designees will conduct accountability of study product (KPI-121 or placebo). 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. Study product shipment records will be verified by comparing the shipment inventory sheet to the actual quantity of drug received at the site. Accurate records of receipt and disposition of the study product (e.g., dates, quantity, subject number, dose dispensed, returned) must be maintained by the Investigator or his/her designee. Study product will be stored in a secure area with limited access at 15-25°C/59-77°F with upper limit excursions to 30°C /86°F allowed.

At the end of the study, all study materials, including any unused study product (KPI-121 study product or placebo), as well as original containers (even if empty), will be returned to the drug packaging vendor in accordance with sponsor or designee's standard operations procedures (SOPs), following approval by the Sponsor. All returns of study 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 study product assignments. 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 study product assignment will be revealed on a subject-by-subject basis with the approval of the medical monitor and sponsor, thus leaving the masking of the remaining subjects intact.

A randomization code will be computer-generated by Kala Pharmaceuticals, Inc. or its 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 study product assignments.

7. ASSESSMENT OF EFFICACY

Efficacy Assessments include the following:

- Slit Lamp Biomicroscopy examination of the following ocular signs of inflammation:
  - Signs of anterior ocular inflammation (i.e., cells; 0-4 Scale and flare; 0-4 Scale)
- Subject-Rated Ocular Pain Assessment (0-5 Scale)
- Rescue therapy

8. ASSESSMENT OF SAFETY

8.1. SAFETY PARAMETERS

Safety parameters include:

- Assessments of AEs
- Snellen Distance VA by Pinhole Method
- Slit Lamp Biomicroscopy including assessment of the following signs of inflammation: Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
- IOP Measurement
- 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. 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 1.0% ophthalmic suspension that is unexpected and is determined to be related or possibly related to investigational product, all sites will be notified by the sponsor and each site should report it to its IRB.

9. STATISTICS

9.1. STATISTICAL METHODS

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

9.1.1. Subject Disposition, Demographic and Background Characteristics

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

9.1.2. Analysis of Efficacy

The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all subjects randomized. A subset of efficacy analyses will be repeated using data from those subjects who were randomized, completed 14 days of study product use, had complete data at Visit 5 (Day 8 ± 1 day) and did not have significant protocol deviations, the Efficacy Evaluable (EE) population. Rescued subjects will be included in the EE population if they did not have significant protocol deviations.

The primary analysis of all ophthalmic efficacy measures will be based on a single study eye for each subject. Each subject's study eye will be defined as the surgery eye. The set of primary endpoints, using hierarchical statistical testing, is (1) proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension and placebo, and (2) proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Visit 5 (Day 8 ±1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension and placebo.

The following scoring scale for anterior chamber cells will be used:
0 = No cells seen
1 = 1 - 5 cells
2 = 6 - 15 cells
3 = 16 - 30 cells
4 = greater than 30 cells

The following scoring scale for ocular pain will be used:
0 = None
1 = Minimal
2 = Mild
3 = Moderate
4 = Moderately Severe
5 = Severe

Using the hierarchical testing scheme, the first test will be the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID using the χ^2 statistic.

If this test is statistically significant at the two-sided $\alpha = 0.05$ level in favor of the KPI-121 1.0% ophthalmic suspension group, then the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at Visit 5 (Day 8 ± 1 day) maintained through Visit 6 (Day 15 ± 1 day) without receiving rescue medication prior to Visit 6 (Day 15 ± 1 day) as compared between KPI-121 1.0% ophthalmic suspension dosed BID and placebo dosed BID will be tested using the same statistic.

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 study 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 intensity and relationship to the study product. Ophthalmoscopy findings will be summarized descriptively. IOP measurements, Snellen Distance VA by pinhole method and Slit Lamp Biomicroscopy will be summarized as safety outcomes.

9.2. SAMPLE SIZE ESTIMATION

A two group χ^2 test with a 0.05 two-sided significance level will have 99% power to detect the difference between a proportion with complete resolution of anterior chamber cells in the active group of 0.31 and the placebo group proportion of 0.15 when the sample size in each group is 250. The power is the same for the complete resolution of pain endpoint.

9.3. LEVEL OF SIGNIFICANCE

The primary assessment will be evaluated using a 5% level of significance using the hierarchical testing described in Section 9.1.2 Analysis of Efficacy.

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

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

If more than 5% of data points are missing at the primary analysis time point (Day 8) in any treatment group, a tipping point analysis will be employed to assess the sensitivity of the results to the distribution of the allocation of treatment success and failure to the missing data 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.

9.6. SUBJECTS TO BE INCLUDED IN THE ANALYSIS

Efficacy analysis will be performed for all randomized subjects, the Intent-to-Treat (ITT) population. A subset of the efficacy analysis will be repeated using data from those subjects who were randomized, completed 14-days of study product use, had complete data at Visit 5 (Day 8 $\pm$ 1 day) and did not have significant protocol deviations, the Efficacy Evaluable (EE) population. Rescued subjects will be included in the EE population if they did not have significant protocol deviations. AEs and other safety parameters will be analyzed for all randomized subjects receiving randomized study product (Safety population).

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

Apple DJ, Solomon KD, Tetz MR, Assia EI, Holland EY, Legler UF, Kostick AM. Posterior capsule opacification. Survey of ophthalmology. 1992;37:73–116.

Leopold IH. Nonsteroidal and steroidal anti-inflammatory agents. In: Sears M, Tarkkanen A, editors. Surgical Pharmacology of the Eye. New York, NY: Raven Press; 1985:83–133

Tennant JL. Cystoid maculopathy: 125 prostaglandins in ophthalmology. In: Emery JM, editor. Current Concepts in Cataract Surgery: Selected proceedings of the fifth biennial cataract surgical congress, Section 3. St. Louis, MO: CV Mosby; 1978:360–362.

16. APPENDICES

APPENDIX 1: SUMMARY OF EVENTS

Procedures	Visit 1 Screening -14 to -1 days	Visit 2 Surgery Day 0	Visit 3 Randomization Day 1	Visit 4 Study Visit Day 4 (±1 day)	Visit 5 Study Visit Day 8 (± 1 day)	Visit 6 End of Study Product Use Visit Day 15 (± 1 day)	Visit 7 Follow-Up Day 18 (± 1 day)
Informed Consent, HIPAA Authorization and Medical/Ophthalmic History	X						
Subject-Rated Ocular Pain Assessment			X	X	X	X	X
Concomitant Medication Query	X	X	X	X	X	X	X
Pregnancy Test[a]	X					X	
Inclusion/Exclusion	X		X				
AE Assessment		X[b]	X	X	X	X	X
Surgery		X					
Snellen Distance Pinhole Visual Acuity	X		X	X	X	X	X
Slit Lamp Biomicroscopy	X		X	X	X	X	X
IOP Measurement	X		X	X	X	X	X
Dilated Ophthalmoscopy	X					X	
Randomization			X				
Study Product Administration in Clinic			X				
Dispense Study Product			X				
Collect Study Product						X	
Dosing Compliance Assessment				X	X	X	

[a]Women of childbearing potential only; [b]Assessments of AEs pre-surgery and post-surgery

APPENDIX 2: SUBJECT-RATED OCULAR PAIN ASSESSMENT

In the clinic, subjects will be handed a laminated card on which is printed the Subject-Rated Ocular Pain Assessment. Each subject will be asked to subjectively rate their pain at Visit 3 to 7 based on this scale. This information will be provided to study personnel to enter into the subject's source documentation. The grading scale for pain to be used will be as follows:

0 = None:	Absence of positive sensation.
1 = Minimal:	Presence of mild sensation or discomfort typical of postoperative surgery (e.g., diffuse or focal foreign body sensation, mild transient burning or stinging, etc.)
2 = Mild:	Mild, tolerable aching of the eye.
3 = Moderate:	Moderate or more prolonged aching sufficient to require the use of over the counter (OTC) analgesics (e.g. acetaminophen).
4 = Moderately Severe:	More prolonged aching requiring the use of an OTC analgesic other than acetaminophen.
5 = Severe:	Intense ocular, periocular or radiating pain (e.g. constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics.

APPENDIX 3: SNELLEN DISTANCE PINHOLE VISUAL ACUITY

VA measurement will be performed with the Snellen eye chart using pinhole at a distance of 20 feet (6 meters). VA will be assessed at all study visits except the surgery visit (Visit 2).

APPENDIX 4: SLIT LAMP BIOMICROSCOPY

The biomicroscopy exam will be performed at every visit (except Visit 2/Surgery) with the slit lamp using a beam of 1.0 mm height and 1.0 mm width with the beam at maximum luminance and using the high powered lens if using Haag-Streit model slit lamp. If alternate model used, site to assure a 1.0 mm by 1.0 mm window with high magnification is achieved.

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

Anterior Chamber

Cells

0 = No cells seen
1 = 1 - 5 cells
2 = 6 - 15 cells
3 = 16 - 30 cells
4 = greater than 30 cells

Flare

0 = None
1 = Mild (trace to clearly noticeable, visible)
2 = Moderate (without plastic aqueous humor)
3 = Marked (with plastic aqueous humor)
4 = Severe (with fibrin deposits and/or clots)

Hyphema:

0 = Absent
1 = Mild
2 = Moderate
3 = Severe

Conjunctiva

Bulbar Conjunctival Injection
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

Palpebral Conjunctival Erythema
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

Cornea

Edema
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

Sclera

Ciliary Flush
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

APPENDIX 5: IOP MEASUREMENT

IOP measurements will be performed utilizing Goldmann applanation tonometery according to the Investigator's standard procedure. All pressure will be recorded in mmHg. IOP assessments will occur at all study visits except the surgery visit (Visit 2).

APPENDIX 6: 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. For each subject, the Investigator will determine whether direct or indirect ophthalmoscopy will be used. 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.

APPENDIX 7: DOSING DIARY

Subjects will be asked to record each day the following information related to administration of study drug:

- Date
- Time of Administration