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Study ID:
KPI-121-C-001

Study Title:
A Phase III, Double-Masked, Randomized, Controlled Trial of KPI-121 in Postsurgical Inflammation

Date:
21 Jul 2014

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-001
Incorporating Amendment 1, Clarification Letter 1, Amendment 2, and Amendment 3

Project:	KPI-121
Compound Number/Name:	KPI-121
Protocol Number:	KPI-121-C-001
Protocol Title:	A Phase III, Double-Masked, Randomized, Controlled Trial of KPI-121 in Postsurgical Inflammation
Sponsor:	Kala Pharmaceuticals, Inc. 100 Beaver Street, Suite 201 Waltham, MA 02453
Medical Monitor:	[redacted]
Issue Date:	Original: 10 Dec 2013 Amendment 1: 28 Mar 2014 Clarification Letter 1 and Amendment 2: 18 Jun 2014 Amendment 3: 21 Jul 2014
Approved:	21 Jul 2014

[redacted]

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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:	A Phase III, Double-Masked, Randomized, Controlled Trial of KPI-121 in Postsurgical Inflammation
Objectives:	The primary objective of the study is: • To investigate the efficacy and safety of KPI-121 ophthalmic suspension compared to placebo in subjects who have undergone cataract surgery. The secondary objective of the study is: • To investigate the comparative efficacy and safety of two different concentrations and two different dosing regimens of KPI-121.
Study Population:	The study population will consist of subjects who have undergone routine uncomplicated cataract surgery and experience ocular inflammation postoperatively.
Number of Subjects	Up to 500 subjects who are candidates for cataract surgery will be screened. One study eye from approximately 402 subjects will be randomized.
Study Products:	KPI-121 drug products (0.25% and 1.0%) or placebo solutions (A and B) will be supplied as study product.
Route and Duration of Administration	Study product will be instilled in the study eye only. Study groups include KPI-121 drug product 0.25% four times a day (QID), KPI-121 drug product 1.0% two times a day (BID), Placebo A QID and Placebo B BID. Study product will be administered for 14 days.
Study Design:	This is a Phase III, multicenter, double-masked, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of two doses and two dosing regimens of KPI-121 ophthalmic suspension versus placebo in subjects who require treatment of postoperative anterior ocular inflammation. Approximately 500 subjects will be screened and up to 402 subjects with one study eye each will be randomized in this study at approximately 25 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 four study groups in an approximate 2:2:1:1 ratio to one of two doses of KPI-121 drug product (0.25% QID or 1.0% BID) or Placebo A or B QID or BID. Drug product or placebo will be initiated on the day following surgery and instilled as one to two drops

	in the study eye according to the assigned dosing regimen for 14 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 four study groups and will initiate study 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 study product will be administered upon completion of 14 days of evaluation. Following the End of Study Product Use Visit (Visit 6; Day 15 ±1 day), subjects will be asked to return to the clinic on Day 17-19 for Visit 7 (Follow-Up) and will be released from the study.
	
	Assessments in this study will include:
	
	• Subject-Rated Ocular Pain assessment (Appendix 2)
	• Snellen Distance Visual Acuity (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
	• Intraocular Pressure (IOP) Measurement (Appendix 5)
	• Dilated Ophthalmoscopy (Appendix 6)
	• Rescue Therapy Assessment
	• Concomitant Medication Use Assessment
	• Assessments of Adverse Events (AEs)

Efficacy Endpoints	**Primary Efficacy Endpoints:** The primary endpoints of this study will be evaluated using hierarchical statistical testing in the following sequence: (1) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo; (2) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo; (3) the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo; and (4) the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo. **Secondary Efficacy Endpoints:** The proportion of study eyes with complete resolution (grade = 0) of anterior chamber cells (scale 0-4) and complete resolution (grade = 0) of pain (scale 0-5) at Day 8. The proportion of study eyes with complete resolution (grade = 0) of anterior chamber cells (scale 0-4) and complete resolution (grade = 0) of pain (scale 0-5) at Day 15. Mean grade of anterior chamber cells (scale 0-4) at Day 8. Mean pain grade (scale 0-5) at Day 8. Mean grade of anterior chamber cells (scale 0-4) at Day 15. Mean pain grade (scale 0-5) at Day 15.
Safety Endpoints	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 study product or until completion of the subject's first menstrual cycle following the last administration of the study 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 study product or until completion of the subject's first menstrual cycle following last administration of the study 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 study product or until completion of the subject's

first menstrual cycle following last administration of the study 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 study product or until completion of the subject's first menstrual cycle following administration of the study product, whichever period of time is longer.

NOTE: For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following administration of the study 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 study product or until completion of the subject's first menstrual cycle following administration of the study 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), 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 study product) within 14 days prior to cataract surgery and for the duration of the study 4. Require concurrent ocular therapy with immunosuppressants (e.g., Restasis®) within 30 days prior to surgery and for the duration of the study. 5. Require change in treatment with anticholinergics, systemic immunosuppressive agents, oral steroids (dose must be less than 11 mg/day) 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 study 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. 10. Use any topical eyelash growth medications within 7 days prior to surgery and for the duration of the study 11. Use TNF-blocking agents (e.g., etanercept, adalimumab, infliximab) within 2 days prior to surgery and for the duration of the study 12. Have history of glaucoma, IOP >21 mmHg at the screening or randomization visit(s), or are being treated for glaucoma in either eye. 13. Wear contact lenses for 4 weeks prior to Visit 1 and throughout the study. 14. Be monocular or have Snellen Distance VA by pinhole method of 20/200 or worse in the non-study eye. 15. Have had penetrating intraocular surgery in the study eye within 3 months or within two weeks in the fellow eye. 16. Have had selective laser trabeculoplasty (SLT) within 3 months prior to surgery. 17. Have had corneal refractive surgery, glaucoma surgery, or corneal transplantation (full thickness, anterior, or posterior) within the past year or are unstable and/or

	require medication. 18. 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. 19. Have been exposed to an investigational drug within 30 days prior to screening or up to 18 days following surgery. 20. 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. 21. Have a known history of alcohol and/or drug abuse. 22. 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
QID	Four Times Daily
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 drug products. Preclinical studies have shown improved pharmacokinetics for KPI-121 compared to Lotemax, with prolonged drug presence on the ocular surface and increased drug penetration into ocular tissues. This improved pharmacokinetic profile has the potential to reduce 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. Study KPI-121-C-001 will help establish the optimal dosing strength and dosing frequency.

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 white, controlled-drop polyethylene tip and a polypropylene cap. The bottle will be a 7.5 mL dropper bottle; the fill volume will be determined after manufacturing trial runs, and will be in the range of 5.0 to 6.0 mL of product.

For this trial, KPI-121 drug product will be supplied in two strengths: 0.25% and 1.0%. Each milliliter of KPI-121 0.25% drug product contains 2.5 mg loteprednol etabonate as the active ingredient; each milliliter of KPI-121 1.0% drug product contains 10 mg loteprednol etabonate as the active ingredient. Inactive ingredients in KPI-121 drug products ar [redacted] as preservative. KPI-121 suspensions are essentially isotonic and are buffered to maintain a power of hydrogen (pH) of 5.0 – 7.0.

There are two placebo controls that have the same composition as KPI-121 drug products but do not contain loteprednol etabonate. Placebo A contains [redacted]. Both placebo controls also contain [redacted] as preservative. The placebo controls are essentially isotonic and are buffered to maintain pH 5.0 – 7.0. They are sterile, aqueous solutions supplied in the same white, low-density polyethylene plastic bottle with the same white, controlled-drop polyethylene tip and white polypropylene closure as KPI-121 drug products.

1.2. JUSTIFICATION FOR ROUTE OF ADMINISTRATION AND DOSE SELECTION

KPI-121 will be administered as a topical ophthalmic suspension. This clinical study will be used to determine the optimal dosing strength and dosing frequency for the commercial product.

Subjects are expected to self-administer one to two drops of either KPI-121 drug product or placebo control according to the dosing schedule appropriate to the study group to which the subject is assigned.

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 dose effect and tolerability for 14 days across two dosing concentrations and two dosing regimens of KPI-121 drug products: 0.25% QID and 1.0% 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

Up to 500 subjects who are candidates for cataract surgery will be screened. One study eye from approximately 402 subjects who have undergone routine uncomplicated cataract surgery and experience ocular inflammation postoperatively will be randomized.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. PRIMARY OBJECTIVE

The primary objective of the study is:

- To investigate the efficacy and safety of KPI-121 drug product compared to placebo in subjects who have undergone cataract surgery.

2.2. SECONDARY OBJECTIVES

The secondary objective of the study is:

- To investigate the comparative efficacy and safety of two different concentrations and two different dosing regimens of KPI-121.

3. TRIAL DESIGN

3.1. ENDPOINTS

3.1.1. Efficacy Endpoints

3.1.1.1. Primary Efficacy Endpoints

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

(1) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo;

(2) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo;

(3) the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo; and

(4) the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo.

3.1.1.2. Secondary Efficacy Endpoints

- The proportion of study eyes with complete resolution (grade=0) of anterior chamber cells (scale 0-4) and complete resolution (grade=0) of pain (scale 0-5) at Day 8.
- The proportion of study eyes with complete resolution (grade=0) of anterior chamber cells (scale 0-4) and complete resolution (grade=0) of pain (scale 0-5) at Day 15.
- Mean grade of anterior chamber cells (scale 0-4) at Day 8.
- Mean pain grade (scale 0-5) at Day 8.
- Mean grade of anterior chamber cells (scale 0-4) at Day 15.
- Mean pain grade (scale 0-5) at Day 15.

3.1.2. Safety Endpoints

3.1.2.1. Safety Endpoints

- 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

3.2. DESCRIPTION OF STUDY AND DURATION OF PARTICIPATION

3.2.1. Description of Trial Design

This is a Phase III, multicenter, double-masked, randomized, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of two doses and two dosing regimens of KPI-121 versus placebo in subjects who require treatment of postoperative anterior ocular inflammation. Approximately 500 subjects will be screened and up to 402 subjects with one study eye each randomized in this study at approximately 25 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 four study groups in an approximate 2:2:1:1 ratio:

- KPI-121 0.25% QID
- KPI-121 1.0% BID
- Placebo A QID
- Placebo B BID

Dosing of study product will be initiated on the day following surgery and instilled as one to two drops in the study eye according to the assigned dosing regimen for 14 days. The first dose of study 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 study product administration, no other information or discussion regarding the subject's assigned study product or regimen 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 four study groups and will initiate study 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), and Visit 6 (Day 15 ±1). The last dose of study product will be administered upon completion of 14 days of evaluation. Following

the End of Study Product Use Visit (Visit 6), subjects will be asked to return to the clinic on Days 17-19 for Visit 7 for follow-up and then will be released from the study.

A summary of events is provided in Appendix 1. 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).

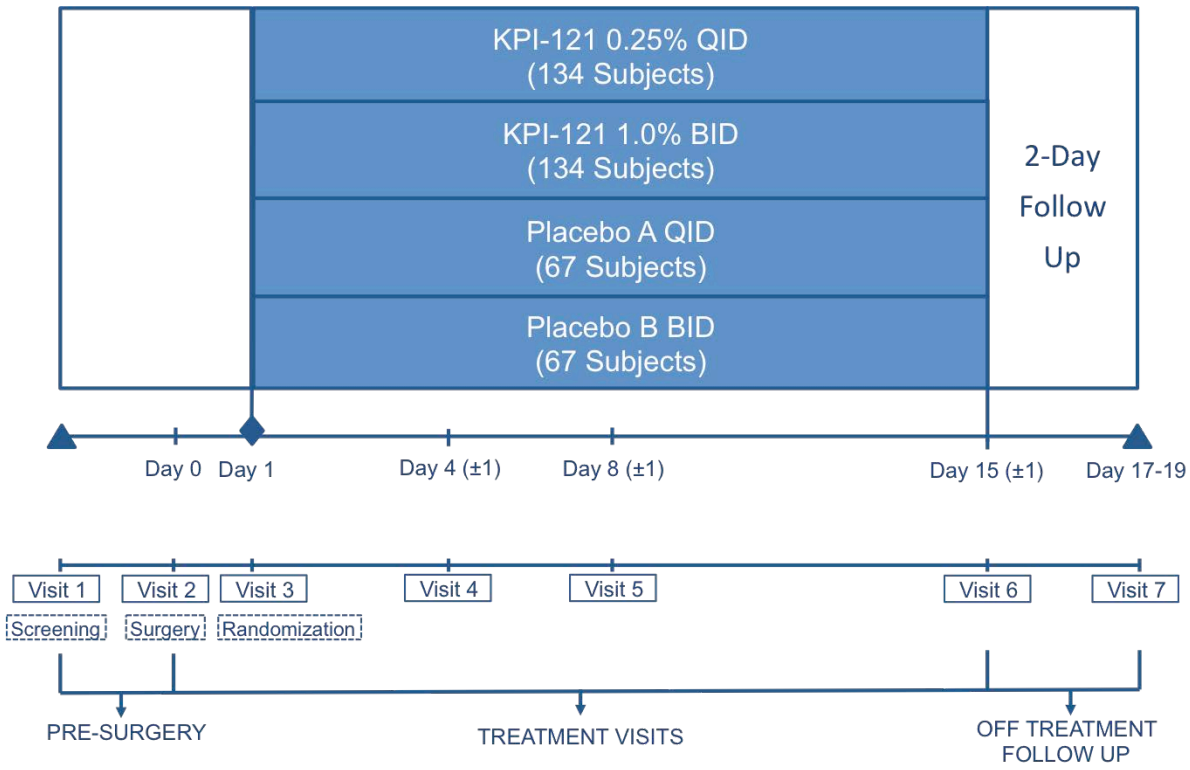

FIGURE 1: STUDY SCHEMATIC

3.2.2. Study Product

KPI-121 drug product will be supplied in two strengths: 0.25% and 1.0% as a suspension in identically packaged opaque dropper bottles. KPI-121 drug product is a sterile, aqueous, submicron suspension of loteprednol etabonate 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.

Subjects randomized to placebo control arms will receive the same bottles containing all components at the concentrations used in the KPI-121 drug product with the exception of the active component, loteprednol etabonate. Prior to each instillation of study product, subject will shake the study product bottle.

TABLE 1: COMPOSITIONS OF KPI-121 DRUG PRODUCTS

Ingredient	Function	0.25% Drug Product	1.0% Drug Product
		Concentration (% w/v)	
Loteprednol etabonate	Active pharmaceutical ingredient	0.25	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]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

TABLE 2: COMPOSITION OF PLACEBO A AND PLACEBO B

Ingredient	Function	Placebo A	Placebo B
		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]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

The study product kit consists of a box of randomized study product that contains two dropper bottles of study product. At Visit 3, eligible subjects will receive one bottle of study product. The second bottle will be retained at the site and provided to the subject, in the event the subject needs additional study product during the treatment period. The box label will contain the following information: sponsor name, protocol and medicinal number, storage temperature and required statement(s) per the appropriate regulatory agency. The dropper bottle contained within the box will be labeled with the following information: sponsor name, protocol number and medicinal number.

The study product will be stored in a secure area with limited access at controlled room temperature (15-25°C/59 -77°F). Subjects will be instructed to shake the study 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) or four (QID) daily doses. Subjects will then self-administer either one (BID) or three (QID) additional doses of study product during the remainder of that day. Visit 3 should be scheduled in the morning to allow subjects to receive a full day of either BID or QID dosing.

On all other study evaluation days, subjects in the BID group will be asked to instill one (1) "Morning Dose" and one (1) "Evening Dose" approximately 12 hours following the previous dose. Subjects in the QID group will be asked to instill one (1) dose upon awakening and then three (3) subsequent doses approximately four (4) hours after their previous dose. The four (4)

doses in the QID group will be described as "Morning Dose," "Mid-Morning Dose," "Afternoon Dose," and "Evening Dose."

3.2.3. Methods to Minimize Bias

To minimize bias, the following measures will be taken:

Study product allocation (placebo versus drug product) 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 AND WITHDRAWAL 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 study product or until completion of the subject's first menstrual cycle following the last administration of the study 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 study product or until completion of the subject's first menstrual cycle following last administration of the study 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 study product or until completion of the subject's first menstrual cycle following last administration of the study 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 study product or until completion of the subject's first menstrual cycle following administration of the study product, whichever period of time is longer.

       NOTE: For Depo-Provera injection contraceptives, the statement regarding first menstrual cycle following administration of the study 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 study product or until completion of the subject's first menstrual cycle following administration of the study 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), 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 study product) within 14 days prior to cataract surgery and for the duration of the study
4. Require concurrent ocular therapy with immunosuppressants (e.g., Restasis®) within 30 days prior to surgery and for the duration of the study.
5. Require change in treatment with anticholinergics, systemic immunosuppressive agents, oral steroids (dose must be less than 11 mg/day) 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 study 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.
10. Use any topical eyelash growth medications within 7 days prior to surgery and for the duration of the study
11. Use TNF-blocking agents (e.g., etanercept, adalimumab, infliximab) within two days prior to surgery and for the duration of the study
12. Have history of glaucoma, IOP >21 mmHg at the screening or randomization visit(s), or are being treated for glaucoma in either eye.
13. Wear contact lenses for 4 weeks prior to Visit 1 and throughout the study.

14. Be monocular or have Snellen Distance VA by pinhole method of 20/200 or worse in the non-study eye.
15. Have had penetrating intraocular surgery in the study eye within 3 months or within two weeks in the fellow eye.
16. Have had selective laser trabeculoplasty (SLT) within 3 months prior to surgery.
17. Have had corneal refractive surgery, glaucoma surgery, or corneal transplantation (full thickness, anterior, or posterior) within the past year or are unstable and/or require medication.
18. 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.
19. Have been exposed to an investigational drug within 30 days prior to screening or up to 18 days following surgery.
20. 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.
21. Have a known history of alcohol and/or drug abuse.
22. 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).

4.4. SUBJECT WITHDRAWAL CRITERIA

Any subject who wishes to withdraw from the study on his or her own accord for any reason is entitled to do so without obligation. The Investigator may remove any subject from the study, if it is deemed necessary.

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 subject should remain in the study and continue to be evaluated at the regularly scheduled visits. In the event study discontinuation of a randomized subject is necessary, the Investigator should make every attempt to have subject complete Visit 6 assessments and/or follow through until Investigator deems the reason for study discontinuation has resolved, if applicable. If a non-serious adverse event (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.

Subjects who withdraw from the study will not be replaced.

5. PROCEDURES

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

5.1. VISIT DESCRIPTION

5.1.1. Visit 1: 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:

- Each subject that is screened will be assigned a Subject Identification (ID) consisting of a three-digit Investigator number plus a three-digit number starting with number 001. The Subject ID will be used as the primary subject identifier for the duration of the study
- Non-ocular and ocular medical history
- Concomitant medication usage and medications taken during the 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

Instructions to subject:

- Subjects will be informed of the date and time for their cataract surgery
- Subjects will be asked to return for Visit 2/Surgery as scheduled within 14 days

5.1.2. Visit 2: Surgery Visit (Day 0)

Pre-surgical Procedures:

This visit will occur no more than 14 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.

- The subject will receive routine post-surgical care and instructions for the cataract surgery as determined by the Investigator.
- Medications routinely administered prior to and following cataract surgery will be collected in the source and CRF. These medications will be indicated for routine cataract surgery and are not expected to be associated with treatment for AEs unless otherwise indicated.
- The subject will be instructed 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 either BID or QID dosing of study 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:

- Use of any concomitant medications since the last visit
- 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.)
- Subject-Rated Ocular Pain Assessment
- 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

NOTE: All ocular assessments must be performed in each eye.

- Upon verification of study eligibility (Section 4.3), all eligible subjects will be randomized to receive four times per day dosing of either 0.25% KPI-121 drug product or Placebo A **OR** two times per day dosing of either 1.0% KPI-121 drug

product or Placebo B. The following will be performed for all randomized subjects:

- The first dose of double-masked study product will be administered in the clinic under the supervision of designated study personnel. Prior to administration of study product, subjects will be reminded on the proper method for instillation including but not limited to shaking study product bottle prior to each instillation. Since subjects will receive one (1) dose of study product in the clinic, they will self-administer at most three (3) additional doses of study product on the first day if assigned to the QID groups or one (1) additional dose of study product if assigned to the BID dosing group.

- Assess the occurrence of any AEs after study product administration
- Study product kits and instructions for administration will be dispensed
- Subjects will be scheduled 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 3 or 4 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
- Subject-Rated Ocular Pain Assessment
- Snellen Distance VA by pinhole method
- Slit Lamp Biomicroscopy:
  - Signs of anterior ocular inflammation (i.e., cell and flare grading)
  - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
- IOP Measurement
- Dosing compliance will be reviewed and assessed. If needed, the second bottle of study product will be dispensed to the subject.
- Subjects will be asked to return for Visit 5 on Day 8 ±1.

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

This visit will occur on Day 8 ±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
- Subject-Rated Ocular Pain Assessment
- Snellen Distance VA by pinhole method
- Slit Lamp Biomicroscopy:

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

- IOP Measurement
- Dosing compliance will be reviewed and assessed. If needed, the second bottle of study product will be dispensed to the subject.
- Subjects will be asked to discontinue study product upon return for Visit 6 on Day 15 ±1.

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

The end of study product use visit will occur on Day 15 ±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
- Collect used and unused study product
- UPT
- Subject-Rated Ocular Pain Assessment
- Snellen Distance VA by pinhole method
- Slit Lamp Biomicroscopy
  - Signs of anterior ocular inflammation (i.e., cell and flare grading)
  - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
- IOP Measurement
- Dilated Ophthalmoscopy
- Dosing compliance will be reviewed and assessed.

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 17-19 for Visit 7.

5.1.7. Visit 7: Follow-Up Visit (Days 17-19)

This follow-up visit will occur on Day 17 to 19 and the following will be performed/assessed:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Subject-Rated Ocular Pain Assessment
- Snellen Distance VA by pinhole method

- Slit Lamp Biomicroscopy
    - Signs of anterior ocular inflammation (i.e., 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:

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- UPT
- Used and unused study product collected and compliance assessed via the daily dosing information recorded by the subject.
- Subject-Rated Ocular Pain Assessment
- Snellen Distance VA by pinhole method
- Slit Lamp Biomicroscopy
    - Signs of anterior ocular inflammation (i.e., cell and flare grading)
    - Palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, bulbar conjunctival injection
- IOP Measurement
- Dilated Ophthalmoscopy

5.2. DISCONTINUATION CRITERIA

Study product use may be discontinued and any subject may be withdrawn 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. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

In the event that discontinuation of study product is necessary, the Investigator will make every attempt to complete all subsequent safety and efficacy assessments. The reason for premature discontinuation should be entered onto the CRF and recorded in the subject chart.

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.

6. TREATMENT OF SUBJECTS

6.1. STUDY PRODUCTS TO BE ADMINISTERED

KPI-121 drug product (0.25% or 1.0%) 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 controlled room temperature (15-25°C/59-77°F).

Subjects will be asked to administer study product either twice or four times each day depending on assignment. Prior to each instillation of study product, subject will be instructed to shake study product bottle. The subjects will record daily, the time of administration of each dose of study product (Appendix 7). Compliance with instillation of study product will be reviewed and assessed at each clinic visit.

6.2. CONCOMITANT MEDICATIONS

All medications 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.
- Medications routinely administered and not explicitly prohibited in this protocol used prior to and following uncomplicated cataract surgery are allowed. These medications will be collected in the source and eCRF as indicated for routine cataract surgery and are not expected to be associated with treatment for AEs unless otherwise indicated.

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)
- Mast cell stabilizers
- Antihistamines
- Decongestants

- All eye drops (except antibiotic eye drops considered to be included in post cataract surgery standard of care treatment)
- Glaucoma medications
- All topical ophthalmic gels or artificial tears
- TNF-blocking agents (e.g., etanercept, adalimumab, infliximab)

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 immunosuppressant (e.g., Restasis®)
- Other investigational products

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

- Anticholinergics
- Antidepressants (stable dose of PRN treatment acceptable)
- Systemic immunosuppressive agents
- Oral steroids (dose must be less than 11 mg/day)

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 at controlled room temperature (15-25°C/59-77°F) in an area limited with controlled access.

At the end of the study, all study materials, including any unused study product (KPI-121 drug 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 D.A.T.A., 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 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)
- 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.

> **NOTE:** Events that are related and expected due to uncomplicated cataract surgery should not be classified as an AE.

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 study 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 study product use.

Unlikely:

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

Possible:

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

Probable:

- Reasonable temporal relationship with study 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 study 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

Typically, the time that the informed consent is signed by the subject is designated as the start of safety data collection.

If a subject will not formally enter a trial until several days or longer after the informed consent is signed, the day of randomization to treatment may be a more appropriate time to begin collecting safety information. AEs occurring prior to randomization may be more appropriately considered medical history or pre-existing conditions.

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, intensity, seriousness, causality (relationship to use of study 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 study 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.

Expected changes resulting from routine uncomplicated cataract surgery will not be captured as AEs. Likewise, the presence of inflammation due to surgery is not an AE but rather the condition under investigation.

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. Study product start date
5. Date of last dose of study product
6. Date study product reinitiated (if study 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 study product
    - Action taken with study 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 study product
12. Copy of AE page from the CRF

NOTE: If an SAE occurs in any study involving KPI-121 that is unexpected and is determined to be related or possibly related to study product, all sites will be notified by the sponsor and each site should report it to their IRB.

8.5. 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 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).

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.

If the two placebo groups demonstrate no statistically significant difference, they will be pooled for analysis.

9.1.1. Subject Disposition, Demographic and Background Characteristics

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

9.1.2. Analysis of Efficacy

The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all subjects randomized. A subset of efficacy analyses will be examined for the Efficacy Evaluable (EE) population defined as all subjects who were randomized, completed 14 days of study product use, had complete data at the Day 8 visit and 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) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo; (2) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo;; (3) the difference in the proportion of study eyes with complete resolution of pain (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo; and (4) the difference in the proportion of study eyes with complete resolution of pain (grade=0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to 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

If the two placebo groups demonstrate no statistically significant difference, they will be pooled for analysis.

Using the hierarchical testing scheme, the first test will be the difference in the proportion of study eyes with complete resolution of **anterior chamber cells** (grade = 0) at postoperative Day 8 between the pooled placebo control group and the KPI-121 0.25% QID group using the chi-squared statistic.

If this test is statistically significant at the two-sided alpha = 0.05 level in favor of the KPI-121 0.25% QID group, then the difference in the proportion of study eyes with complete resolution of **anterior chamber cells** (grade = 0) at postoperative Day 8 between the pooled placebo control group and the KPI-121 1.0% BID group will be tested using the same statistic.

If this test is statistically significant at the two-sided alpha = 0.05 level in favor of the KPI-121 1.0% BID group, then the difference in the proportion of study eyes with complete resolution of **pain** (grade = 0) at postoperative Day 8 between the pooled placebo control group and the KPI-121 1.0% BID group will be tested using the same statistic.

If this test is statistically significant at the two-sided alpha = 0.05 level in favor of the KPI-121 1.0% BID group, then the difference in the proportion of study eyes with complete resolution of **pain** (grade = 0) at postoperative Day 8 between the pooled placebo control group and the KPI-121 0.25% QID group will be tested using the same statistic.

Secondary endpoints will be the proportion of study eyes with complete resolution (grade = 0) of anterior chamber cells (scale 0-4) and complete resolution (grade = 0) of pain (scale 0-5) at Day 8 and at Day 15.

Additional secondary endpoints are composite mean scores of anterior chamber cell and pain grades which will be summarized for each study group at each visit.

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 chi-squared test with a 0.05 two-sided significance level will have 91% power to detect the difference between a proportion of responders in either of the active dosing regimen groups of 0.31 and a combined placebo group proportion of 0.14 when the sample size in each group is 134.

9.3. LEVEL OF SIGNIFICANCE

The primary assessment of the dose-response with 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

Any missing, unused, or spurious data will be noted in the final clinical study report. Multiple imputation will be employed to analyze incomplete data sets under the assumption that missing data are, at worst, characterized as missing at random (MAR). The reasons for missing data will be recorded and the impact of these reasons and any treatment group imbalance on the assumption of MAR will be evaluated.

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 ITT population) with at least one post-baseline (baseline = Visit 3) assessment. A subset of the efficacy analysis will be repeated using data from those subjects completing 14-days of study product use, fulfilling all study visits and achieving reasonable compliance with the study protocol (the EE population). 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 study product receipt, storage, disposition, and regulatory files related to the study. Monitors or designees will also assess the ongoing suitability of the investigative site throughout the study.

12. ETHICS

12.1. Institutional Review Board

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

Any modification of study procedures or amendments to the protocol must be approved by the IRB prior to implementation. In the event that a modification or amendment is considered by the Investigator to be immediately necessary to ensure subject safety, the Investigator will promptly notify their 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 Good Clinical Practices (GCP) meeting 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	Visit 2 Surgery	Visit 3 Randomization	Visit 4 Study Visit	Visit 5 Study Visit	Visit 6 End of Study Product Use Visit	Visit 7 Follow-Up
	-14 to -1 days	Day 0	Day 1	Day 4 (±1 day)	Day 8 (± 1 day)	Day 15 (± 1 day)	Days 17 - 19
Informed Consent, HIPAA Authorization and Medical History	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					
Subject-Rated Ocular Pain Assessment			X	X	X	X	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 the Subject-Rated Ocular Pain Assessment to subjectively rate their pain at Visit 3 to 7. 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