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Study ID:
KPI-121-C-010

Study Title:
Safety and Efficacy of KPI-121 1% Ophthalmic Suspension Versus Prednisolone Acetate Ophthalmic Suspension 1% for the Treatment of Inflammation Following Cataract Surgery in Children 0 to 3 Years of Age

Date:
11 Jul 2018

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-010

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Compound Number/Name:	KPI-121 1%
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Sponsor:	Kala Pharmaceuticals, Inc. 100 Beaver St, Suite 201 Waltham, MA 02453
Medical Monitor:	[redacted]
Issue Date:	Original: 14 Nov 2017 Amendment 1: 19 Dec 2017 Amendment 2: 16 Mar 2018 Amendment 3: 11 Jul 2018

Approved by:

[redacted]

KALA PHARMACEUTICALS, INC.
Clinical Protocol KPI-121-C-010
Investigator Signature Page

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For Serious Adverse Event Reporting:	[redacted]
For Serious Adverse Event Questions:	[redacted]

Investigator Name (printed or typed):

_____

Investigator's Signature:

_____ _____
Date

SYNOPSIS

Study Title:	Safety and Efficacy of KPI-121 1% Ophthalmic Suspension versus Prednisolone Acetate Ophthalmic Suspension 1% for the Treatment of Inflammation Following Cataract Surgery in Children 0 to 3 Years of Age
Objectives:	To compare the safety and efficacy of KPI-121 1% ophthalmic suspension (KPI-121 1%) dosed twice daily versus prednisolone acetate ophthalmic suspension 1% (prednisolone acetate 1%) dosed four times daily in children 0 to 3 years of age following cataract surgery.
Study Population:	The study population will consist of pediatric subjects from 0 through 3 years of age who have undergone routine, uncomplicated cataract surgery.
Number of Subjects:	Approximately 120 subjects who are candidates for cataract surgery will be screened. One study eye from approximately 60 subjects will be randomized.
Investigational Products:	KPI-121 1% and vehicle or prednisolone acetate 1% will be supplied as investigational product.
Route and Duration of Administration:	Subjects will be randomized to either: • 1-2 drops of KPI-121 1% and vehicle dosed two times per day each for a total of four times per day (QID) instilled in the study eye for 29 days ± 2 days post-surgery, starting at the first post-operative assessment. This may be followed by treatment or taper using a commercially available product as determined by the Investigator. **OR** • 1-2 drops of prednisolone acetate 1% dosed QID instilled in the study eye for 29 days ± 2 days post-surgery, at the first post-operative assessment. This may be followed by treatment or taper using a commercially available product as determined by the Investigator.
Study Design:	This is a Phase 3B, multicenter, double-masked, randomized, parallel-group, active-controlled study designed to evaluate the safety and efficacy of KPI-121 1% versus prednisolone acetate 1% in controlling postoperative inflammation in children 0 to 3 years of age who have undergone cataract surgery. Approximately 120 subjects who are candidates for cataract surgery will be screened.

	Subjects who meet all eligibility criteria and undergo routine, uncomplicated, cataract surgery will be randomized into this study at approximately 20 centers located in the United States (US). Subjects will be randomized into one of two study groups in an approximate 1:1 ratio. Subjects will be randomized to either: o **BOTH** KPI-121 1% ophthalmic suspension **AND** KPI-121 vehicle dosed BID each for 29 days ± 2 OR o Prednisolone acetate ophthalmic suspension 1% dosed QID for 29 days ± 2 days. Dosing with investigational product will be initiated at the first post-operative assessment and will be instilled as one to two drops in the surgery eye according to the assigned dosing regimen for 29 ± 2 days. This may be followed by treatment or taper using a commercially available product as determined by the Investigator. This study will include 6 clinic visits as well as the surgery visit over 35 to 53 days total study duration. Visit 1 (Screening) will occur between 14 and 1 day(s) prior to surgery. Subjects who meet preoperative screening inclusion/exclusion criteria will be entered into the study. On the day of surgery, subjects will undergo routine cataract surgery according to the Investigator's normal procedures. At the first post-surgery assessment, which may be later on the same day of surgery or the following day, eligibility regarding inclusion and exclusion criteria will be confirmed and subjects will be randomized to one of the two treatment arms. The first dose of investigational product will be administered in the clinic, and parents/guardians will be instructed how to dose and record investigational product use. This will be considered Day 1 (Visit 2). Following randomization, subjects' parents/caregivers will be instructed to return to the clinic to be evaluated on Day 8 ± 2 days (Visit 3), Day 15 ± 2 days (Visit 4), Day 29 ± 2 days (Visit 5), and Day 36 ± 2 days (Visit 6). Additional investigational product will be dispensed at Visit 4. Investigational product will be discontinued at Visit 5. Used investigational product kits will be collected by the study staff at Visits 4 and 5. At Visit 5 further treatment or taper with a commercially available product may be given as determined by the Investigator. Additionally, a phone contact will be made between Visits 4 and 5 (Day 21-23) to assess subject progress. Subjects will return for a Follow-Up/Safety Visit on Day 36 ± 2 days (Visit 6).

	Assessments in this study will include (when obtainable): • Medical History Review • Age Appropriate Visual Acuity (VA) • Signs of anterior chamber ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as vitritis and wound integrity • Symptoms of anterior ocular inflammation – photophobia and lacrimation • Intraocular Pressure (IOP) Measurement • Dilated Ophthalmoscopy • Modified Global Assessment of Postoperative Inflammation • Rescue Therapy Assessment • Assessment of Concomitant Medication Use • Assessment of Adverse Events (AEs) • Dosing Compliance Assessment/Dosing Diary Review
Efficacy Evaluation:	**Primary Efficacy Evaluation:** 1. The proportion of study eyes with anterior chamber cell grade = 0 at Visit 4 (Day 15 ± 2 days) without receiving rescue medication prior to Visit 4 as compared between the KPI-121 1% dose BID and the prednisolone acetate 1% dosed QID treatment arms. **Secondary Efficacy Evaluation:** 1. The proportion of study eyes with a Modified Global Overall Assessment of Postoperative Inflammation Score = 0 at Visit 4 (Day 15 ± 2 days) without receiving rescue medication prior to Visit 4 as compared between the KPI-121 1% BID and the prednisolone acetate 1% QID treatment arms. **Statistical Analysis:** The efficacy and safety analyses will be based on a single study eye for each subject. Each subject's study eye will be defined as the surgery eye. All statistical analyses will be performed using Statistical Analysis System (SAS) software.

	The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all subjects randomized and with at least one post-baseline assessment. A subset of efficacy analyses, the Per Protocol (PP) population, will be repeated using data from those subjects who were randomized, completed 15 days ± 2 days of investigational product use, had complete data at Visit 4 (Day 15 ± 2 days), and did not have significant protocol deviations. Rescued subjects will be included in the PP population if they did not have significant protocol deviations: however, these subjects will be considered treatment failures. No inferential statistical analyses are planned. Data will be summarized using descriptive statistics only. Assessment of efficacy will be based primarily on the number and percentage of subjects in each treatment group with an anterior chamber cell grade of 0 at Visit 4 (Day 15 ± 2 days) with no need for rescue medication through Visit 4 and, secondarily, on the Modified Global Overall Assessment of Postoperative Inflammation score of 0 at Visit 4 (Day 15 ± 2 days) without receiving rescue medication prior to Visit 4. The individual components of the Global Assessment score will also be evaluated (i.e., number and percentage of subjects in each treatment group in each score category at each visit).
Safety Evaluations:	Assessment of AEs Change from baseline to each post-surgery visit in ocular signs: • Visual Acuity • IOP Measurement • Dilated Ophthalmoscopy (at Visits 1 and 5 only) Assessment of safety will be based on the assessment of AEs. To allow for at least a 95% chance of detecting an AE with a 10% incidence rate, a minimum sample size of 30 subjects per group (KPI-121 1% or prednisolone acetate 1%) is required.
Eligibility Criteria:	**Inclusion Criteria:** At Visit 1, individuals of either gender and any race will be eligible for study participation if they:

1. Have informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization provided by parent or guardian prior to any study-related procedures.
2. Are 0-3 years of age (have not had their 4th birthday) as of the date of surgery.
3. Are candidates for routine, uncomplicated, cataract surgery
    a. With or without capsulotomy and vitrectomy
    b. With or without posterior chamber intraocular lens (IOL) implantation
    c. But not combined with any other surgery.
4. Have a unilateral cataract or have bilateral cataracts and are candidates for surgery:
    a. On the first eye, and surgery on the second eye is not planned until after the subject completes participation in the study **OR**
    b. On the second eye, and surgery on the first eye was uncomplicated,any post-operative inflammation has resolved and anterior chamber cell and flare grades both = 0.

Exclusion Criteria:

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

1. Have a post-traumatic cataract.
2. Have suspected permanent low vision or blindness in the fellow non-study eye.
3. Have active uveitis in either eye.
4. Have an ocular neoplasm in either eye.
5. Have the presence of any active or suspected viral, bacterial, or fungal disease in the either eye.
6. Have a history of glaucoma, ocular hypertension, steroid-induced IOP rise or have an IOP >21 mmHg in either eye at the screening or randomization visit(s).
7. Require the use of any topical ophthalmic medication in the study eye within 2 days prior to surgery and for the duration of the study, except for drops that are needed to examine the eye or to prepare for and undergo surgery as well as post-operative antibiotic drops. **NOTE**: Besifloxacin Ophthalmic Suspension is not permitted within 2 days prior to surgery or for the duration of the study.

	8. Require the use of systemic or ocular non-steroidal anti-inflammatory drugs within 2 days prior to surgery and for the duration of the study. 9. Require treatment with systemic, inhaled, or ocular corticosteroids within 14 days prior to surgery and for the duration of the study with the exception of intraoperative ocular corticosteroids. 10. Require a change in use of nutraceuticals or multivitamins within 2 days prior to surgery and for the duration of the study. 11. Have known hypersensitivity or contraindication to the investigational product(s) or their components. 12. Have a diagnosis of: a) Severe/serious ocular condition that in the judgment of the Investigator could confound study assessments or limit compliance. b) Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance. 13. Have been exposed to an investigational product within 30 days prior to surgery. **Randomization Criteria:** To qualify for randomization at Visit 2 (1st post-surgery assessment which may be later on the day of surgery or the following day), a subject must: 1. Have undergone routine, uncomplicated, cataract surgery, with or without capsulotomy and/or anterior vitrectomy and with or without posterior chamber IOL implantation. 2. Continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions and medications. 3. Continue to have IOP $\leq$ 21 mmHg in both eyes.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AR	Adverse Reaction
BID	Twice Daily
°C	Degrees Celsius
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
°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
LE	Loteprednol etabonate
LDPE	Low-Density Polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mmHg	Millimeter of Mercury
PDF	Portable Document Format
pH	Potential of Hydrogen
PP	Per Protocol
QID	Four Times Daily
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SAS	Statistical Analysis System
SOPs	Standard Operating Procedures
US	United States of America
USP	United States Pharmacopeia
VA	Visual Acuity
w/v	Weight to Volume

1. INTRODUCTION

The most frequent surgery in ophthalmology is cataract extraction and intraocular lens (IOL) implantation in adult patients with age-related cataracts. Most controlled clinical trials evaluating the anti-inflammatory activity of topical corticosteroids have been conducted in this patient population and have demonstrated efficacy in the treatment of both inflammation and pain following cataract surgery.

Children also experience cataracts, which are often treated via surgery, although the incidence is significantly less than in adults. Pediatric cataract is a major cause of preventable childhood blindness, affecting approximately 200,000 children worldwide, with an estimated prevalence ranging from three to six per 10,000 live births (Foster, Gilbert, & Rahi, 1997; Holmes, Leske, Burke, & Hodge, 2003; Stayte, Reeves, & Wortham, 1993). Pediatric cataracts are characterized as congenital if present within the first year of life, developmental if present after infancy, or traumatic if caused by injury.

As in adults, the most common treatment for cataract in the pediatric population is cataract extraction. Pediatric cataract surgery has historically been associated with a high incidence of postoperative inflammation, which is most commonly treated with topical corticosteroids (Sharma, Pushker, Dada, Vajpayee, & Dada, 1999; Zwaan, Mullaney, Awad, Al-Mesfer, & Wheeler, 1998). Although improvements in surgical techniques and IOL design have improved outcomes in pediatric cataract surgery, postoperative inflammation is still a concern for these patients (Medsinge & Nischal, 2015). Topical corticosteroids are generally considered to have significant anti-inflammatory activity in pediatric patients, despite a dearth of controlled studies in this population. In the American Academy of Ophthalmology Pediatric Ophthalmology Education Center's publication 'Pediatric Cataracts: Overview' the following is stated: "Prednisolone eye drops are the mainstay of treatment to control severe inflammation, which is generally inevitable" (Wilson, 2016).

1.1. DESCRIPTION OF INVESTIGATIONAL PRODUCT

KPI-121 1% contains submicron particles of loteprednol etabonate (LE) suspended in a formulation consisting of excipients that have been used in other FDA-approved ophthalmic products. Each mL of KPI-121 1% ophthalmic suspension contains 10 mg loteprednol etabonate as the active ingredient. [redacted] Kala Pharmaceuticals, Inc. is

developing this novel loteprednol etabonate formulation for the treatment of postoperative anterior segment inflammation and pain.

KPI-121 vehicle has the same excipient composition as KPI-121 1% ophthalmic suspension with the exception of the active drug, LE.

Pred Forte® (prednisolone acetate ophthalmic suspension, USP) 1%, an approved glucocorticoid product, will be purchased and supplied to sites as the active comparator product. Pred Forte® contains prednisolone acetate (microfine suspension) 1% as the active ingredient. Inactive ingredients are benzalkonium chloride (as preservative); boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate. The pH during its shelf life ranges from 5.0 - 6.0.

For additional details on toxicology studies and the respective safety profiles, see the KPI-121 Investigator's Brochure and the Pred Forte® package insert.

1.2. JUSTIFICATION FOR ROUTE OF ADMINISTRATION AND DOSE SELECTION

KPI-121 1% and prednisolone acetate 1% will be administered as topical ophthalmic suspensions. Direct instillation into the eye 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. KPI-121 1% dosed BID has been shown to be safe and effective in adults (Kim, Gupta, Holland and Brazzell, 2018). Prednisolone acetate 1% dosed QID has been shown to be safe and effective in both adults and children (Wilson, 2016).

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 120 subjects, from 0 - 3 years of age, who are candidates for cataract surgery will be screened. The surgical/study eye from approximately 60 subjects who have undergone routine, uncomplicated, cataract surgery, with or without capsulotomy and vitrectomy and with or without posterior chamber intraocular lens (IOL) implantation, but not combined with any other surgery, will be randomized and evaluated at approximately 20 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% ophthalmic suspension given BID compared to prednisolone acetate ophthalmic suspension 1% given QID in pediatric subjects who have undergone routine, uncomplicated cataract surgery.

3. TRIAL DESIGN

3.1. PRIMARY EFFICACY EVALUATION

The primary efficacy evaluation is the proportion of study eyes with anterior chamber cell grade = 0 at Visit 4 (Day 15 ± 2 days) without receiving rescue medication prior to Visit 4 as compared between the KPI-121 1% dosed BID and the prednisolone acetate 1% dosed QID treatment arms.

3.2. SECONDARY EFFICACY EVALUATION

The secondary efficacy evaluation is the proportion of study eyes with a Modified Global Overall Assessment of Postoperative Inflammation Score = 0 at Visit 4 (Day 15 ± 2 days) without receiving rescue medication prior to Visit 4 as compared between the KPI-121 1% BID and the prednisolone acetate 1% QID treatment arms.

3.3. SAFETY ENDPOINTS

Safety evaluations will include:

- Assessment of AEs
- Visual Acuity
- IOP Measurement
- Dilated Ophthalmoscopy (assessed at visits 1 and 5 only)

Ocular assessments will be summarized at each post-surgery and compared between the KPI-121 1% dosed BID and the prednisolone acetate 1% dosed QID treatment arms.

3.4. DESCRIPTION OF TRIAL DESIGN

This is a Phase 3B, multicenter, double-masked, randomized, parallel-group, active-controlled study designed to evaluate the safety and efficacy of KPI-121 1% versus prednisolone acetate 1% in pediatric subjects who undergo cataract surgery. Approximately 120 subjects, from 0 - 3 years of age, who are candidates for cataract surgery will be screened. Approximately 60 subjects, after undergoing routine, uncomplicated, cataract surgery, will be randomized into this study at approximately 20 centers located in the US.

Subjects who meet all eligibility criteria will be randomized to one of two treatment arms in an approximate 1:1 ratio:

- KPI-121 1% BID **AND** vehicle BID, to support the masking of the investigational product
- Prednisolone acetate 1% QID

Dosing of investigational product will be initiated at the first post-surgery assessment, Visit 2 (Day 1), instilled as 1-2 drops in the study eye. The first dose of investigational product will be administered by the subject's parent/caregiver under the supervision of a dedicated dosing coordinator who is otherwise uninvolved in the assessment or evaluation of the subject.

This study will include up to 6 clinic study visits and a phone contact and 35 to 53 days total study duration. Visit 1 (Screening) will occur between 14 and 1 day(s) prior to surgery and subjects who meet preoperative screening inclusion/exclusion criteria will be entered into the study. On the day of Surgery, subjects will undergo routine cataract surgery according to the Investigator's normal procedures. The first post-surgery assessment, which may be later on the same day of surgery or the following day will be considered Visit 2 (Day 1). At this visit, subjects who continue to meet the eligibility criteria will be randomized to one of the two study groups and will initiate dosing with investigational product. Following randomization, the subject's parent/caregiver will be instructed to instill investigational product in the study eye four times a day (QID) for 29 days ± 2 days up until Visit 5. The subject will return to the clinic to be evaluated at Visit 3 (Day 8 ± 2 days), Visit 4 (Day 15 ± 2 days) and Visit 5 (Day 29 ± 2 days/End of Investigational Product Use Visit). A phone contact will be made between Visits 4 and 5 (Day 21 -23) to assess subject progress.

Investigational product will be discontinued and collected at Visit 5. This may be followed by treatment or taper using a commercially available product as determined by the Investigator. Subjects will return for a follow up visit, Visit 6 (Day 36 ± 2 days) then will be released from the study.

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

- Medical History Review
- Visual Acuity, (Snellen, Optotype recognition, Central/Steady/Maintained with Fix and Follow or Fix and Follow alone per the subject's age and as determined by the Investigator and used for all study visits for the subject) (Appendix 2)
- Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon, as well as vitritis and wound integrity, (Slit lamp biomicroscopy, ophthalmoscopy or light examination depending on subject's tolerance. The method used for these

assessments will be determined by Investigator and used for all study visits for the subject) (Appendix 3)
- Symptoms of anterior ocular inflammation – photophobia and lacrimation
- IOP Measurement (Appendix 4)
- Dilated Ophthalmoscopy (Appendix 5)
- Modified Global Overall Assessment of Postoperative Inflammation (Appendix 6)
- Rescue Therapy Assessment
- Concomitant Medication Use Assessment
- Assessment of Adverse Events
- Dosing Compliance Assessment/Dosing Diary Review (Appendix 7)

A study schematic follows (Figure 1).

FIGURE 1: STUDY SCHEMATIC

Screening	**Surgery**	**Treatment** KPI-121 1% Ophthalmic Suspension + KPI-121 vehicle (30 Subjects) / **Treatment** Prednisolone Acetate 1% Ophthalmic Suspension (30 Subjects)					**Follow-Up**
Visit 1	Cataract Surgery	Visit 2 Day 1 (day of surgery or following day)	Visit 3 Day 8 ± 2 days	Visit 4 Day 15 ± 2 days	Phone Contact Day 21-23 days	Visit 5 Day 29 ± 2 days	Visit 6 Day 36 ± 2 days
-14 to -1 days prior to surgery		Randomization	Treatment	Treatment	Treatment	End of IP Use	Off Study
No Dosing	No Dosing	First use of IP QID Dosing	QID Dosing	QID Dosing	QID Dosing	Last Dosing	No Dosing

3.4.1. Investigational Product

KPI-121 1% ophthalmic suspension is a sterile, aqueous, submicron suspension of loteprednol etabonate (LE). Each mL of KPI-121 1% ophthalmic suspension contains 10 mg of LE as the active ingredient. [redacted]

[redacted]

KPI-121 1% ophthalmic suspension will be supplied in a white, low-density polyethylene (LDPE) bottle with a controlled-drop, linear low-density polyethylene tip and a pink, high-density polyethylene cap. The dropper bottle also has a white LDPE tamper-evident overcap which, when removed, exposes the pink screw cap for opening the bottle and dispensing the product. KPI-121 1% is supplied as a minimum fill of 2.8 mL in a 5-mL bottle.

KPI-121 vehicle will be supplied in the same type of bottle/tip/cap configuration and will contain all components at the concentrations used in the KPI-121 1% ophthalmic suspension with the exception of the active component, LE.

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]		

TABLE 2: COMPOSITION OF KPI-121 VEHICLE

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

Pred Forte® (prednisolone acetate ophthalmic suspension, USP) 1% contains the active ingredient prednisolone acetate (microfine suspension) 1%. Other ingredients include benzalkonium chloride as a preservative; boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate. The exact concentrations of excipients are unpublished. The pH during its shelf life ranges from 5.0 - 6.0.

Pred Forte® (prednisolone acetate ophthalmic suspension, USP) 1% will be supplied as 1 ml of sterile aqueous suspension in opaque white 5 mL LDPE plastic dropper bottles with white, high impact polystyrene caps. The commercial bottle label will be over-wrapped to cover the commercial label, and then a masked clinical trial label will be applied to the overwrap. masked clinical trial label.

Subjects' parents/caregivers will be instructed to shake the investigational product bottle well before every use.

The randomized investigational product kits to be dispensed will consist of a box with four dropper bottles, labeled Bottle 1 through Bottle 4.

At Visit 2, eligible subjects' parents/caregivers will receive an investigational product kit containing four bottles. Parents/caregivers will be instructed to dose with 1-2 drops of Bottle 1 in the morning, followed by 1-2 drops of Bottle 2 at midday, 1-2 drops of Bottle 3 in the afternoon, and 1-2 drops of Bottle 4 at bedtime. This treatment schedule will be followed for 29 days ± 2 days. All bottles should be stored upright and shaken well before dosing.

Subjects randomized to KPI-121 1% will receive investigational product kits containing both KPI-121 1% (Bottles 1 and 4) and vehicle (Bottles 2 and 3). Thus, the treatment schedule will result in QID dosing with 2 of the doses KPI-121 1% and 2 of the doses vehicle.

Subjects randomized to prednisolone acetate 1% will receive kits with 4 bottles of prednisolone acetate 1%, for QID dosing.

Subject's parent/caregiver will return their kits (and bottles) and receive a new kit containing the same product at Visit 4 to ensure sufficient investigational product through Visit 5. At Visit 5 they will return their second kit and end investigational product use. Completion of investigational product use may be followed by treatment or taper with a commercially available product as determined by the Investigator.

All kit labels and dropper bottle labels will contain the following information: sponsor name, protocol and kit number, storage temperature, and required statement(s) per the appropriate regulatory agency. The dropper bottle labels will also be printed with the bottle number (e.g., Bottle 1, Bottle 2, etc.).

Subjects' parents/caregivers will be instructed to shake the investigational product bottle well prior to administering each dose. When subjects receive the first dose administered in the clinic, the dose will count as one of the daily doses. Parents/caregivers will then administer the additional doses of investigational product later that day, according to the dosing schedule and instructions provided by the dosing coordinator.

The Investigator will store all investigational product upright in a secure area, with limited access, at controlled room temperature (15-25°C/59 -77°F). Parents/caregivers will be instructed to store the investigational product upright at room temperature.

3.4.2. Methods to Minimize Bias

To minimize bias, the following measures will be taken:

- Investigational product assignment (KPI-121 1% ophthalmic suspension or prednisolone acetate ophthalmic suspension 1%) will be randomized and masked to the sponsor, subjects, and investigative staff with the exception of a dedicated dosing coordinator. The dedicated dosing coordinator will manage drug dispensing and return, parent/caregiver instruction and initial dosing and will review the dosing diary. Since the KPI-121 1% ophthalmic suspension is only dosed BID, it will be supplemented with BID dosing of vehicle to support the masking.
- The randomization schedule will be generated by the randomization statistician (who is not on the project team) or designee and maintained via the electronic data capture system (EDC) used for the trial.

4. SELECTION OF SUBJECTS

4.1. SUBJECT INCLUSION CRITERIA

At Visit 1, individuals of either gender and any race will be eligible for study participation if they:

1. Have informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization provided by a parent or guardian prior to any study-related procedures.
2. Are 0-3 years of age (have not had their 4th birthday) as of the date of surgery.
3. Are candidates for routine, uncomplicated, cataract surgery
    a. With or without capsulotomy and vitrectomy
    b. With or without posterior chamber intraocular lens (IOL) implantation
    c. But not combined with any other surgery.
4. Have a unilateral cataract or have bilateral cataracts and are candidates for surgery:
    a. On the first eye, and surgery on the second eye is not planned until after the subject completes participation in the study OR
    b. On the second eye, and surgery on the first eye was uncomplicated, any post-operative inflammation has resolved and anterior chamber cell and flare grades both = 0.

4.2. SUBJECT EXCLUSION CRITERIA

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

1. Have a post-traumatic cataract.
2. Have suspected permanent low vision or blindness in the fellow non-study eye.
3. Have active uveitis in either eye.
4. Have an ocular neoplasm in either eye.
5. Have the presence of any active or suspected viral, bacterial, or fungal disease in either eye.
6. Have a history of glaucoma, ocular hypertension, steroid-induced IOP rise or have an IOP >21 mmHg in either eye at the screening or randomization visit(s).
7. Require the use of any topical ophthalmic medication in the study eye within 2 days prior to surgery and for the duration of the study, except for

drops that are needed to examine the eye or to prepare for and undergo surgery as well as post-operative antibiotic drops. **NOTE**: Besifloxacin Ophthalmic Suspension is not permitted within 2 days prior to surgery or for the duration of the study.

8. Require the use of systemic or ocular non-steroidal anti-inflammatory drugs within 2 days prior to surgery and for the duration of the study.
9. Require treatment with systemic, inhaled or ocular corticosteroids within 14 days prior to surgery and for the duration of the study with the exception of intraoperative ocular corticosteroids.
10. Require a change in use of nutraceuticals or multivitamins within 2 days prior to surgery and for the duration of the study.
11. Have known hypersensitivity or contraindication to the investigational product(s) or their components.
12. Have a diagnosis of:
    a. Severe/serious ocular condition that in the judgment of the Investigator could confound study assessments or limit compliance.
    b. Severe/serious systemic disease or uncontrolled medical condition that in the judgment of the Investigator could confound study assessments or limit compliance.
13. Have been exposed to an investigational product within 30 days prior to surgery.

4.3. RANDOMIZATION CRITERIA

To qualify for randomization at Visit 2 (1st post-surgery assessment which may be later on the day of surgery or the following day), a subject must:

1. Have undergone routine, uncomplicated, cataract surgery, with or without capsulotomy and/or anterior vitrectomy and with or without posterior chamber IOL implantation and not combined with any other surgery.
2. Continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions and medications.
3. Continue to have IOP $\leq$ 21 mmHg in both eyes.

5. PROCEDURES

Written informed consent and HIPAA authorization will be obtained from each subject's parent/guardian 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 Surgery. After obtaining written informed consent and HIPAA authorization, site staff will perform/assess the following in the order suggested below:

- Assign each screened subject a Subject Identification (ID) number consisting of a three-digit Investigator number plus a four-digit number starting with number 1001. The Subject ID will be used as the primary subject identifier for the duration of the study.
- Collect the following information and perform the following assessments (when obtainable) (**NOTE:** All ocular assessments must be performed in both eyes):
  - Non-ocular and ocular medical history
  - Medications taken during the 30 days prior to screening and concomitant medication usage
  - Visual acuity (Snellen, Optotype recognition, Central/Steady/Maintained with Fix and Follow or Fix and Follow alone per the subject's age and as determined by the Investigator and used for all study visits for the subject)
  - Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as vitritis and wound integrity (Slit lamp biomicroscopy, ophthalmoscopy or light examination depending on subject's tolerance. The method used for these assessments will be determined by Investigator and used for all study visits for the subject)
  - Symptoms of anterior ocular inflammation - photophobia and lacrimation
  - IOP measurement
  - Dilated Ophthalmoscopy
  - Inclusion/exclusion criteria evaluation
- Ensure subjects to return for surgery in no more than 14 days.

5.1.2. Surgery

Pre-surgical Procedures:

Cataract surgery will occur no more than 14 days and no less than 1 day after Visit 1 and the following will be performed:

- Routine pre-surgical care and procedures as determined by the Investigator

Surgical Procedure

The surgeon will perform his or her routine cataract surgical procedures.

Post-Surgical Procedures

- Routine post-surgical care and instructions will be provided by the Investigator.
- Medications routinely administered prior to, during and immediately following cataract surgery will be collected as a summary document and included as a source document but not listed in the EDC. Only non-routine medications will be collected as concomitant medications in the subject's source document and eCRF.

5.1.3. Visit 2: First Post-Operative Assessment Visit (This may be later on the day of surgery or the following day. This will be considered Day 1)

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

- Review use of any concomitant medications since Visit 1
- Assess occurrence of any additional medical or ophthalmic history since Visit 1
- Perform (when obtainable):
  - Visual acuity assessed using the same method used at the screening visit
  - Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as vitritis and wound integrity assessed using the same method used at the screening visit

  - Symptom assessment of anterior ocular inflammation – photophobia and lacrimation
  - IOP measurement
- Subjects whose surgery is confirmed to have been routine and who continue to meet inclusion/exclusion criteria with respect to current ocular and medical conditions and medications, including having intraocular pressures ≤ 21 mmHg in both eyes, will be randomized to receive either KPI-121 1% ophthalmic suspension dosed BID AND vehicle dosed BID or prednisolone acetate ophthalmic suspension 1% dosed QID.
- Randomization will be performed through the EDC system.

Initiation of Dosing

- Dispense the investigational product kit according to the randomization results.
- The dedicated dosing coordinator will review the investigational product kit, bottles, dosing times and proper method for instillation including but not limited to shaking investigational product bottle prior to each instillation with the parent/guardian and provide written instructions.
- Provide the Dosing Diary and review instructions for completion.
- The parent/guardian will administer the first dose of double-masked investigational product, in the study eye in the clinic under the supervision of a designated dosing coordinator.
- Study staff will assess the occurrence of any AEs after investigational product administration. **NOTE:** Signs and symptoms of inflammation typically seen after uncomplicated, cataract surgery will not be classified as AEs, but rather the condition under study.
- Schedule the subject to return to the clinic on Day 8 ± 2 days for Visit 3.
- Ask parent/guardian to bring the Dosing Diary with them to the next clinic visit.

5.1.4. Visit 3: Study Visit (Day 8 ± 2 days)

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

- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Perform (when obtainable):

  - Visual acuity assessed using the same method used at the screening visit
  - Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as vitritis and wound integrity assessed using the same method used at the screening visit
  - Symptom assessment of anterior ocular inflammation – photophobia and lacrimation
  - IOP measurement
  - Modified Global Overall Assessment of Postoperative Inflammation
- Review dosing compliance/Dosing Diary.
- Instruct parents/caregivers to continue investigational product and return for Visit 4 on Day 15 ± 2 days. Remind them to bring the investigational product kit and Daily Dosing Diary with them.

5.1.5. Visit 4: Study Visit (Day 15 ± 2 days)

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

- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Perform (when obtainable):
  - Visual acuity assessed using the same method used at the screening visit
  - Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as and vitritis and wound integrity assessed using the same method used at the screening visit
  - Symptom assessment of anterior ocular inflammation – photophobia and lacrimation
  - IOP measurement
  - Modified Global Overall Assessment of Postoperative Inflammation
- Review dosing compliance/Dosing Diary.
- Collect initial investigational product Kit and dispense second Kit.
- Instruct parents/caregivers to return for Visit 5 on Day 29 ± 2 days. Remind them to bring the investigational product Kit and Dosing Diary with them.

5.1.6. Mid-Visit Phone Contact (Day 21 - 23)

A phone contact will be made between Visits 4 and 5 (Day 21 -23) to assess subject progress, including but not limited to: continued dosing, adverse events, parent/caregiver questions, concerns and comments.

5.1.7. Visit 5: End of Investigational Product Use (Day 29 ± 2 days)

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

- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Collect investigational product Kit
- Collect diary
- Perform (when obtainable):
  - Visual acuity assessed using the same method used at the screening visit
  - Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as and vitritis and wound integrity assessed using the same method used at the screening visit
  - Symptoms of anterior ocular inflammation - photophobia and lacrimation
  - IOP measurement
  - Dilated ophthalmoscopy
  - Modified Global Overall Assessment of Postoperative Inflammation

Completion of investigational product at Visit 5 may be followed by treatment or taper using a commercially available product as determined by the Investigator. Regardless of treatment and after cessation of investigational product, parents/caregivers will be instructed to return for follow-up on Day 36 ± 2 days for Visit 6.

5.1.8. Visit 6: Follow-Up Visit (Day 36 ± 2 days)

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

- Use of any concomitant medications since the last visit
- Occurrence of any AEs since the last visit
- Perform (when obtainable):
  - Visual acuity assessed using the same method used at the screening visit
  - Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as vitritis and wound integrity assessed using the same method as used at the screening visit
  - Symptom assessment of anterior ocular inflammation - photophobia and lacrimation
  - IOP measurement
  - Modified Global Overall Assessment of Postoperative Inflammation

5.1.9. 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 Early Termination eCRFs should be completed rather than the Unscheduled Visit eCRFs.

5.1.10. Early Termination Visit

In the event of study termination prior to Visit 6 but following Visit 2, every attempt will be made to ensure that the following will be performed/assessed (when obtainable) (**NOTE:** All ocular assessments must be performed in both eyes.):

- Review use of any concomitant medications since the last visit
- Assess occurrence of any AEs since the last visit
- Collect used and unused investigational product and dosing diary
- Perform (when obtainable):

- Visual acuity assessed using the same method used at the screening visit
- Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as and vitritis and wound integrity assessed using the same method used at the screening visit
- Symptom assessment of anterior ocular inflammation – photophobia and lacrimation
- IOP measurement
- Dilated ophthalmoscopy
- Modified Global Overall Assessment of Postoperative Inflammation

5.2. SUBJECT WITHDRAWAL AND/OR DISCONTINUATION

Any parent/guardian who wishes to discontinue their child's investigational product use or withdraw their child 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, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
3. Parent's/guardian's decision to withdraw.
4. Parent's/caregiver's failure to comply with protocol requirements or study related procedures.
5. 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 possible to have the subject complete the Early Termination assessments. The Investigator should make every attempt to follow all serious adverse events (SAEs) to resolution. The reason for premature discontinuation should be recorded in the subject's chart.

Subjects who withdraw from the trial 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. 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.

5.4. RESCUE MEDICATION USE

Any subjects not responding adequately to the investigational product 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 investigational product and continue study participation through Visit 6.

Rescued subjects will be considered treatment failures, and the need for rescue therapy will not be considered an AE. Rescued subjects should not be withdrawn from the study, but rather followed through the end of the study/Visit 6.

6. TREATMENT OF SUBJECTS

6.1. INVESTIGATIONAL PRODUCTS TO BE ADMINISTERED

KPI-121 1% and vehicle or prednisolone acetate 1% will be supplied as investigational product. One Kit of randomized investigational product containing four dropper bottles will be allocated to each subject at Visit 2.

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

Parents/caregivers will be asked to administer investigational product four times daily during the treatment phase. Instillation of the four doses should be spaced throughout the day at the approximate time points of: morning (Bottle 1), midday (Bottle 2), afternoon (Bottle 3), and bedtime (Bottle 4). Prior to each instillation of investigational product, the parent/caregiver will be instructed to shake the investigational product bottle well. The parent/caregiver will record the time of administration and number of drops administered for each dose of investigational product in the Daily Dosing Diary (Appendix 7).

Additional investigational product will be dispensed at Visit 4 and discontinued at Visit 5. Used investigational product kits will be collected by the study staff at Visits 4 and 5.

Compliance with instillation of investigational product will be assessed at each clinic visit and reviewed with the parent/caregiver if poor compliance is noted.

6.2. CONCOMITANT MEDICATIONS

With the exception of peri-operative standard of care medications, all medication that the subject has taken 30 days prior to Visit 1 and through Visit 6 or discontinuation from the study will be recorded in the subject's chart/source documents and the eCRF. The 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 ocular antibiotics at the discretion of the Investigator is allowed (with the exception of besifloxacin). Medications routinely administered (and not explicitly prohibited in this protocol) as part of an uncomplicated cataract surgery

procedure are allowed. These medications will be collected in a summary source document and will not be captured within the eCRF. If there is a change from the standard of care as documented in the source document, the medication will be added to the eCRF. 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 30 days prior to surgery and for the duration of the study:

- Other investigational products.

Within 14 days prior to surgery and for the duration of the study:

- The use of systemic, inhaled or ocular corticosteroids with the exception of intraoperative ocular corticosteroids.

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

- The use of any topical ophthalmic medication in the study eye, except for drops that are needed to examine the eye or to prepare for and undergo surgery, including post-operative antibiotic drops. **NOTE**: besifloxacin ophthalmic suspension is not permitted.
- The use of systemic or ocular non-steroidal anti-inflammatory drugs.
- Change in use of nutraceuticals or multivitamins.

6.3. INVESTIGATIONAL PRODUCT USE COMPLIANCE

Compliance will be assessed using the dosing information recorded in the Daily Dosing Diary completed by the parent/caregiver.

6.4. DRUG ACCOUNTABILITY

The sponsor's study monitors or designees will conduct accountability of investigational product (KPI-121 1%, vehicle, and prednisolone acetate 1%). Accountability will be ascertained by performing reconciliation between the amount of investigational product sent to the site and the amount of used and unused investigational product at the time of reconciliation.

Investigational product will be shipped to the investigational sites under sealed conditions. Investigational product shipment records will be verified by comparing the shipment inventory sheet to the actual quantity of drug received (i.e., kit level accounting) at the site. Accurate records of receipt and disposition of the investigational product (e.g., dates, subject number, kit number dispensed, and kits and bottles returned) must be maintained by the Investigator or his/her designee. Investigational product will be stored upright in a secure area, with limited access, at 15-25°C/59-77°F.

At the end of the study, all investigational product (KPI-121 1%, vehicle and prednisolone acetate 1%), including all used and unused bottles and kits, will be returned to the drug packaging vendor in accordance with sponsor or designee's standard operating procedures (SOPs), following approval by the Sponsor. All returns of investigational product will be documented. The study monitor or designee will verify drug accountability. All drug accounting procedures must be completed before the study is considered complete.

6.5. MAINTENANCE OF RANDOMIZATION AND PROCEDURE FOR BREAKING THE CODE

The sponsor, the project teams at the designated Contract Research Organizations (CROs), and investigative staff responsible for assessments of study endpoints will be masked to investigational product assignments. 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 1%, immediate emergency unmasking is not necessary. If the Investigator feels it is necessary to unmask a subject's assignment after an emergency situation, the Investigator may call the medical monitor and notify the sponsor. The investigational product assignment will be revealed on a subject-by-subject basis with the approval of the medical monitor and sponsor, thus leaving the masking of the remaining subjects intact.

A randomization code for assignment of subjects to treatment arms will be computer-generated by Kala Pharmaceuticals, Inc. or its designee.

Randomization team members, specifically the designated dosing coordinator(s), will work independently of other team members at the site. Study personnel, study subjects, the sponsor, and project teams at the CROs involved in the study will be masked to investigational product assignments.

7. ASSESSMENT OF EFFICACY

7.1. EFFICACY PARAMETERS

Efficacy Assessments include the following:

- Signs of anterior ocular inflammation – cell and flare grading, corneal clarity, conjunctival injection, chemosis, hypopyon as well as vitritis and wound integrity
- Investigator assessment of symptoms of anterior ocular inflammation – photophobia and lacrimation
- Modified Global Overall Assessment of Postoperative Inflammation
- Use of rescue therapy

8. ASSESSMENT OF SAFETY

8.1. SAFETY PARAMETERS

Safety assessments include the following:

- Assessments of AEs
- Visual Acuity
- 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.

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 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.

Definitely:

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

(**NOTE**: Expected changes such as the presence of inflammation resulting from routine uncomplicated cataract surgery will not be captured as AEs.)

8.3. PROCEDURES FOR AE REPORTING BY THE INVESTIGATOR

AEs will be monitored throughout the study. AE reporting will start with the first dose of investigational product. AEs will be reported through the conclusion of Visit 6. AEs 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 has your child felt since their last visit?
- Has your child had any health problems since your last visit?

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 an AE is unresolved at the time of the last 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 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 staff's' attention. In the event of an SAE, the Investigator or site designee must fax the Kala Clinical Study Serious Adverse Event Form within 24 hours of becoming aware of the event to Drug Safety Navigator at Fax: 1-877-684-9387. 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 eCRF

NOTE: If an SAE occurs in any study involving KPI-121 1% 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. Evaluation of Efficacy

The efficacy and safety evaluations will be based on a single study eye, defined as the surgery eye, for each subject.

The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all subjects randomized and with at least one post-baseline assessment. A subset of efficacy analyses will be repeated using data from those subjects who were randomized, completed 15 days ± 2 days of investigational product use, had complete data at Visit 4 (Day 15 ± 2 days), and did not have significant protocol deviations, the Per Protocol (PP) population. Rescued subjects will be included in the PP population if they did not have significant protocol deviations, however, these subjects will be considered treatment failures.

No inferential statistical analyses are planned. Data will be summarized using descriptive statistics only. Assessment of efficacy will be based primarily on the number and percentage of subjects in each treatment group with an anterior chamber cell grade of 0 at Visit 4 (Day 15 ± 2 days) with no need for rescue medication through Visit 4 and, secondarily, on the Modified Global Overall Assessment of Postoperative Inflammation score of 0 at Visit 4 (Day 15 ± 2 days) without receiving rescue medication prior to Visit 4.

The individual components of the Global Assessment score will also be evaluated (i.e., number and percentage of subjects in each treatment group in each score category at each visit).

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 signs and symptoms scoring scales for inflammation will be used:

SIGNS	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anterior Chamber Cells	0 cells	1 - 5 cells	6 - 15 cells	16 - 30 cells	> 30 cells
Anterior Chamber Flare	Absent	Mild (trace to clearly noticeable, visible)	Moderate (without plastic aqueous humor)	Marked (with plastic aqueous humor)	Severe (with fibrin deposits and/or clots)
Corneal Clarity	Absent	Mild	Moderate	Severe	
Conjunctival Injection	Absent	Mild	Moderate	Severe	
Chemosis	Absent	Mild	Moderate	Severe	
Hypopyon	Absent	Mild	Moderate	Severe	
Vitritis	Absent	Mild	Moderate	Severe	
Wound Integrity	Absent	Mild	Moderate	Severe	
SYMPTOMS	Grade 0	Grade 1	Grade 2	Grade 3	
Photophobia	Absent	Mild	Moderate	Severe	
Lacrimation	Absent	Mild	Moderate	Severe	

Modified Global Overall Assessment of Postoperative Inflammation

Based on the signs and symptoms scoring above the following overall categorization of inflammation will be assessed:

0 Clear
1 Improving satisfactorily
2 Not improving or worsening; allow rescue therapy

9.1.3. Analysis of Safety

Analysis of safety data will be presented for all subjects in the Safety population (i.e., all subjects receiving randomized investigational product). AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 21.0) 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 investigational product. Ophthalmoscopy findings will be summarized descriptively. IOP measurements, Visual Acuity and Dilated Ophthalmoscopy assessments will be summarized as safety outcomes.

9.2. SAMPLE SIZE ESTIMATION

Assessment of safety will be based on the assessment of AEs. To allow for at least a 95% chance of detecting an AE with a 10% incidence rate, a minimum sample size of 30 subjects per group (KPI-121 1% or prednisolone acetate 1%) is required. All statistical analyses will be performed using Statistical Analysis System (SAS) software.

9.3. LEVEL OF SIGNIFICANCE

Only descriptive analyses are planned.

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 15) 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

The primary analysis population will be the Intent-to-Treat (ITT) population, defined as all randomized subjects with at least one post-randomization assessment. A subset of efficacy analyses will be repeated using data from those subjects who were randomized, completed 15 days ± 2 days of investigational product use, had complete data at Visit 4 (Day 15 ± 2 days), and did not have significant protocol deviations, the Per Protocol (PP)

population. Rescued subjects will be included in the PP population if they did not have significant protocol deviations.

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 designees 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 trial.

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 trial. 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 will 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 subject's parent/guardian prior to their child undergoing any study-related procedures (prior to or upon Visit 1- Screening). A copy of the signed and dated informed consent document will be given to each parent/guardian. 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 parent/guardian 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

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16. APPENDICES

APPENDIX 1: SUMMARY OF EVENTS

Procedures	Visit 1 Screening	Surgery Day	Visit 2 Study Visit Randomization, 1st Treatment	Visit 3 Study Visit	Visit 4 Study Visit	Phone Contact	Visit 5 End of Investigational Product Use Visit	Visit 6 Follow-Up Visit
	-14 to -1 days to Surgery		Day 1 (May be day of surgery or following day)	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 21 - 23	Day 29 (± 2 days)	Day 36 (± 2 days)
Informed Consent, HIPAA Authorization	X							
Medical/Ophthalmic History	X		X					
Concomitant Medication Review	X		X	X	X		X	X
Age appropriate Visual Acuity	X		X	X	X		X	X
Sign Assessment[a]	X		X	X	X		X	X
Symptom Assessment	X		X	X	X		X	X
IOP Measurement	X		X	X	X		X	X
Dilated Ophthalmoscopy	X						X	
Modified Global Overall Assessment of Postoperative Inflammation				X	X		X	X
Inclusion/Exclusion	X		X					
Surgery		X						
Randomization			X					
Dispense Investigational Product			X		X			
Investigational Product Administration in Clinic			X					
AE Assessment			X[b]	X	X	X	X	X
Dosing Compliance Assessment				X	X		X	
Collect Investigational Product					X[c]		X[d]	

[a] By Slit lamp biomicroscopy, ophthalmoscopy or light exam as necessary, [b]Assessment of AEs starting with first Investigational Product instillation, [c]Collect first kit, [d]Collect second kit

APPENDIX 2: VISUAL ACUITY

Visual acuity (VA) will be assessed using Snellen, Optotype recognition (HOTV or Lea Optotypes), Central/Steady/Maintained with Fix and Follow or Fix and Follow alone per the subject's age and as determined by the Investigator. The same method will be used consistently for each subject.

VA will be assessed at all study visits (when obtainable).

APPENDIX 3: ASSESSMENT OF SIGNS OF ANTERIOR OCULAR INFLAMMATION

Signs of anterior ocular inflammation will be assessed by slit lamp biomicroscopy, ophthalmoscopy or light examination depending on subject's tolerance and as determined by the Investigator. It is recommended that a table-top slit lamp be used if at all possible. The use of a portable slit lamp, ophthalmoscope or muscle light (transilluminator) should be reserved for subjects who cannot comply with the table-top slit lamp exam.
The same method will be used consistently for each subject (when possible).

The signs of anterior ocular inflammation will be performed at every study visit (when obtainable).

The following signs will be assessed:

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

Anterior Chamber 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)

Corneal Clarity
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

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

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

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

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

Wound Integrity (not assessed at Visit 1)
- 0 = Absent
- 1 = Mild
- 2 = Moderate
- 3 = Severe

APPENDIX 4: IOP MEASUREMENT

IOP measurements will be performed utilizing an Icare rebound tonometer, or similar tonometer according to the Investigator's standard procedure. All pressures will be recorded in mmHg.

IOP will be assessed at all study visits (when obtainable, except at Visit 2 when this assessment is required). If unable to obtain a valid measurement by tonometer at Visit 2, assessment by other means, as determined by the investigator, will be accepted.

APPENDIX 5: DILATED OPHTHALMOSCOPY

Dilated ophthalmoscopy will include assessment of vitreous clarity, optic disc, vessels, retina, choroid, macula and periphery. Indirect ophthalmoscopy will be used. 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.

Dilated Ophthalmoscopy will be performed at Visit 1 and Visit 5 (when obtainable).

APPENDIX 6: MODIFIED GLOBAL OVERALL ASSESSMENT OF POSTOPERATIVE INFLAMMATION

SIGNS AND SYMPTOMS OF ANTERIOR OCULAR INFLAMMATION

Signs and symptoms of anterior ocular inflammation will be viewed as a composite to determine the Modified Global Overall Assessment of Postoperative Inflammation.

SIGNS	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anterior Chamber Cells	0 cells	1 - 5 cells	6 - 15 cells	16 - 30 cells	> 30 cells
Anterior Chamber Flare	Absent	Mild (trace to clearly noticeable, visible)	Moderate (without plastic aqueous humor)	Marked (with plastic aqueous humor)	Severe (with fibrin deposits and/or clots)
Corneal Clarity	Absent	Mild	Moderate	Severe	
Conjunctival Injection	Absent	Mild	Moderate	Severe	
Chemosis	Absent	Mild	Moderate	Severe	
Hypopyon	Absent	Mild	Moderate	Severe	
Vitritis	Absent	Mild	Moderate	Severe	
Wound Integrity	Absent	Mild	Moderate	Severe	
SYMPTOMS	Grade 0	Grade 1	Grade 2	Grade 3	
Photophobia	Absent	Mild	Moderate	Severe	
Lacrimation	Absent	Mild	Moderate	Severe	

MODIFIED GLOBAL OVERALL ASSESSMENT OF POSTOPERATIVE INFLAMMATION

Overall Assessment Score

0 Clear
1 Improving satisfactorily
2 Not improving or worsening; allow rescue therapy

Overall Assessment Score will be assessed at Visits 3 - 6.

APPENDIX 7: DAILY Dosing Diary

Parents/caregivers will be provided a Daily Dosing Diary and asked to record the following information related to administration of study drug:

- Date
- Time of administration of each dose
- Number of drops