

Safety and efficacy of twice daily administration of KPI-121 1% for ocular inflammation and pain following cataract surgery

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Terry Kim¹
Kenneth Sall²
Edward J Holland³
R Kim Brazzell⁴
Susan Coultas⁴
Preeya K Gupta¹

¹Department of Ophthalmology, Duke University Eye Center, Durham, NC, USA; ²Sall Research Medical Center, Inc, Artesia, CA, USA;

³Department of Ophthalmology, Cincinnati Eye Institute, University of Cincinnati, Cincinnati, OH, USA; ⁴Kala Pharmaceuticals, Inc, Waltham, MA, USA

Purpose: KPI-121 is a nanoparticle suspension of loteprednol etabonate with improved ocular pharmacokinetics compared with marketed formulations. The efficacy and safety of KPI-121 1% ophthalmic suspension (INVELTYSTM) dosed twice daily (BID) were evaluated in participants who had undergone cataract surgery.

Materials and methods: In two multicenter, randomized, double-masked, parallel-group, vehicle-controlled clinical trials, 386 participants with \geq grade 2 anterior chamber cells (≥ 6 cells) on the day following routine cataract surgery were treated with KPI-121 1% and 325 participants were treated with placebo (vehicle); each group was dosed BID for 2 weeks. Primary efficacy endpoints were complete resolution of ocular inflammation by slit-lamp biomicroscopy and complete resolution of subject-rated ocular pain at Days 8 and 15 with no rescue medication before Day 15. Safety assessments included adverse events (AEs), visual acuity, intraocular pressure measurements, and evaluation of ocular AEs by slit-lamp biomicroscopy and dilated ophthalmoscopy.

Results: Both trials achieved statistical significance favoring KPI-121 1% BID for both primary efficacy endpoints. Combined data analysis showed that significantly more participants treated with KPI-121 vs vehicle achieved complete resolution of anterior chamber cells at Days 8 and 15 ($P \leq 0.0001$) and complete clearing of ocular pain at Days 4, 8, and 15 ($P < 0.0001$). AEs were reported more frequently with vehicle than KPI-121.

Conclusion: KPI-121 1% ophthalmic suspension was effective in resolving postoperative ocular inflammation and pain when dosed BID for 2 weeks in patients following cataract surgery. KPI-121 was found to be safe and well tolerated in both trials.

Keywords: loteprednol etabonate, nanoparticle, mucus penetrating particles, postoperative ocular inflammation, pain

Introduction

Intraocular inflammation is an anticipated sequela of intraocular surgery, such as cataract removal and intraocular lens implantation, and is manifested principally as conjunctival injection, corneal edema, ciliary flush, and aqueous cells and flare. 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 extravasation of protein and cellular blood elements. Untreated inflammation may lead to complications such as cystoid macular edema and corneal scarring.^{1,2} Thus, managing and treating postoperative inflammation is an important goal following cataract surgery.

Current postoperative medication regimens commonly include topical corticosteroids.³ Treatment with corticosteroids is employed to reduce pain and discomfort, and to

Correspondence: RK Brazzell
Kala Pharmaceuticals, Inc, 100
Beaver Street, Suite 201, Waltham,
MA 02453, USA
Tel +1 781 996 5263
Fax +1 781 642 0399
Email kim.brazzell@kalarx.com

facilitate recovery of the blood–aqueous barrier. When administered at the time of surgery and during the immediate postoperative period, corticosteroids can reverse the clinical manifestations of inflammation.⁴ In the US, topical corticosteroids are routinely prescribed with four times daily (QID) dosing for at least 2 weeks following cataract surgery.

KPI-121 1% (INVELTYS™) was developed by Kala Pharmaceuticals, Inc. (Waltham, MA, USA) and recently approved by the US Food and Drug Administration (FDA) for the treatment of postoperative inflammation and pain following ocular surgery.⁵ KPI-121 1% contains loteprednol etabonate (LE) 1% formulated using a proprietary technology known as mucus penetrating particles (MPP). MPP utilizes nanoparticles of drug formulated to enhance penetration of loteprednol through the mucus layer of the tear film, resulting in increased penetration into ocular tissues.

LE was chosen because it is an ester corticosteroid and is rapidly absorbed into ocular tissues. After exerting its effects, loteprednol is rapidly metabolized to inactive metabolites and has been reported to have fewer side effects than traditional glucocorticoids.⁶ Preclinical studies have shown that loteprednol formulated with MPP technology achieved higher ocular exposure than Lotemax® ophthalmic suspension 0.5% (Bausch + Lomb, Rochester, NY, USA), with peak concentrations approximately three-fold higher in ocular tissues and aqueous humor.⁷ The profile of KPI-121 has the potential to deliver potent anti-inflammatory activity with less frequent dosing, while still retaining the safety profile of loteprednol.

The purpose of the current research was to investigate the efficacy and safety of a twice daily (BID) dosing regimen of KPI-121 1% ophthalmic suspension compared to placebo (hereafter referred to as vehicle) in subjects who experienced inflammation following routine, uncomplicated cataract surgery. Herein, the results are presented for two randomized, double-masked, vehicle-controlled, parallel-group trials comparing the safety and efficacy of KPI-121 1% to vehicle in the treatment of subjects with postsurgical inflammation and pain following cataract surgery.

Materials and methods

Patients

These trials included two samples of patients who underwent routine, uncomplicated cataract surgery (eg, phacoemulsification with posterior chamber intraocular lens implantation, not combined with any other surgery), had \geq grade 2 anterior chamber cells (ie, ≥ 6 cells), and had potential postoperative Snellen distance visual acuity (VA) by pinhole method of

at least 20/200 in the study eye. The first trial (hereafter referred to as Trial 1) was conducted at 24 sites (Table S1) within the US between May 2014 and December 2014 and the second trial (hereafter referred to as Trial 2) was conducted at 35 sites (Table S2) within the US between June 2016 and March 2017. Each trial was designed and monitored in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki, and Institutional Review Board approval was obtained by each trial site. Written informed consent was obtained from all subjects at the time of their enrollment and prior to any screening evaluations for the trial.

Individuals of either sex or any race/ethnicity who were ≥ 18 years and were candidates for routine, uncomplicated cataract surgery were eligible for participation in the trials. Patients who required concurrent ocular or non-ocular therapy with any type of medication (eg, nonsteroidal anti-inflammatory drugs, mast cell stabilizers, antihistamines, or decongestants) within 2 days prior to surgery and for the duration of the study were excluded from the trial as were patients with a history of glaucoma, intraocular pressure (IOP) > 21 mmHg at the screening or randomization visit(s), or were being treated for glaucoma in either eye. Also excluded were patients who: 1) had penetrating intraocular surgery in the study eye within 3 months or within 2 weeks in the fellow eye; 2) had selective laser trabeculoplasty within 3 months prior to surgery or had corneal refractive surgery, glaucoma surgery, or corneal transplantation (full thickness, anterior, or posterior) within a year prior to enrollment or were unstable and/or required medication; 3) had active uveitis in either eye or a diagnosis of any type of infection, disease, and/or severe/serious condition that would interfere with study drug effectiveness or study compliance.

Design and treatment

Both studies were randomized, double-masked, parallel-group trials. Randomization was stratified by trial site. In Trial 1, two concentrations and dosing regimens of KPI-121 vs vehicle were administered to one eye for 2 weeks. Subjects were randomized to one of four treatment arms in a 2:2:1:1 ratio: 1) KPI-121 0.25% QID, 2) KPI-121 1% BID, 3) vehicle A QID, 4) vehicle B BID. Following the completion of Trial 1, which demonstrated favorable safety and efficacy profiles for both KPI-121 treatment groups, Trial 2 was initiated to evaluate the safety and efficacy of KPI-121 1% BID compared with vehicle BID administered to one eye for 2 weeks.

As illustrated in Figure 1, subjects in both trials completed up to seven clinic visits (including the surgery day) over 18–33 days of total planned trial duration. Screening occurred

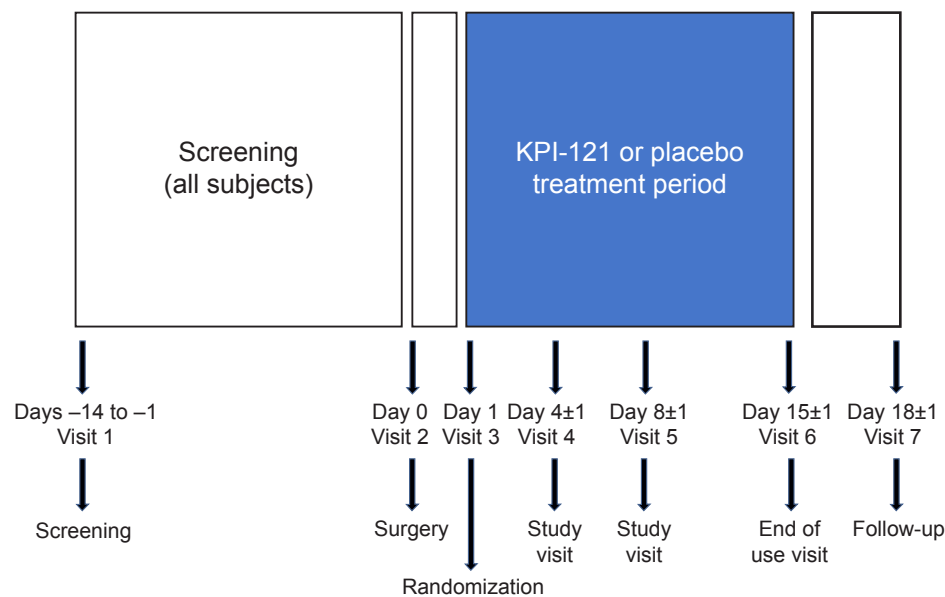


Figure 1 Schematic of the study design.

Notes: In both Trial 1 and Trial 2, subjects completed up to seven clinic visits (including the surgery day) over 18–33 days of total planned trial duration. Screening occurred prior to surgery, and subjects who met preoperative screening inclusion/exclusion criteria were enrolled in the trial. At Day 0 (surgery), subjects underwent routine, uncomplicated cataract surgery according to normal procedures. Randomization occurred on the day following surgery (Day 1). Subjects self-administered 1–2 drops in the study eye (defined as the surgery eye) for 14 days and returned to the clinic to be evaluated at Days 4, 8, and 15. The last dose of study treatment was administered on the morning of the Day 15 visit, upon completion of 14 days of dosing.

between 14 and 1 day(s) prior to surgery, and subjects who met the preoperative screening inclusion/exclusion criteria were allowed to participate in the trial. At Day 0 (surgery), subjects underwent routine, uncomplicated cataract surgery according to normal procedures. Randomization occurred on the day following surgery (Day 1). Subjects who met the qualifying postoperative randomization criteria were eligible for randomization and initiated dosing with study treatment on that day. Subjects self-administered 1–2 drops in the study eye (defined as the surgery eye) for 14 days and recorded dosing information in a daily diary. Following initiation of study treatment dosing, subjects returned to the clinic to be evaluated at Days 4, 8, and 15. The last dose of study treatment was administered on the morning of the Day 15 visit, upon completion of the 14 days of dosing. Following the Day 15 visit, subjects were asked to return to the clinic once between Days 17 and 19 for follow-up and, following completion of all study procedures, were exited from the trial. Efficacy measures were performed on Days 4, 8, and 15. Adverse events (AEs) were assessed across the entire study period.

Primary efficacy endpoints

Anterior chamber cell grade (slit-lamp biomicroscopy)

Ocular inflammation was evaluated by an anterior chamber cell assessment of the study eye performed by the investigator

via slit-lamp biomicroscopy. Investigators rated the subjects' anterior chamber cell grade using a 5-point scale (0= no cells seen; 1=1–5 cells; 2=6–15 cells; 3=16–30 cells; 4=>30 cells). Complete resolution of inflammation was defined as an anterior chamber cell grade =0.

Subject-rated ocular pain assessment

Ocular pain was rated by the subject-rated ocular pain assessment using a 6-point scale (0= none; 1= minimal; 2= mild; 3= moderate; 4= moderately severe; 5= severe). Complete resolution of ocular pain was defined as a grade =0.

Safety evaluation

Safety assessments included evaluation of AEs, Snellen distance VA by pinhole method, IOP measurement, slit-lamp biomicroscopy (palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, and bulbar conjunctival injection), dilated ophthalmoscopy, and use of rescue medication.

AEs

An AE was defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. Treatment-emergent AEs were defined as those events with onset after the first dose of study treatment or, if occurring prior to the first dose, worsened

after administration of the first dose. The severity of AEs was classified as mild, moderate, or severe. The relatedness of AEs to the investigational product was also evaluated. Serious AEs were defined as ones resulting in death or that were life threatening, represented a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, resulted in inpatient hospitalization or prolongation of existing hospitalization, a congenital anomaly/birth defect, or the occurrence of a significant medical event.

Snellen distance VA

Snellen distance VA was assessed at all study visits except the surgery visit (Day 0). VA measurement was performed with the Snellen eye chart using the pinhole at a distance of 20 feet (6 m).

IOP measurement

IOP measurements were performed at all study visits except the surgery visit (Day 0) using Goldmann applanation tonometry according to the investigator's standard procedure.

Slit-lamp biomicroscopy

Slit-lamp biomicroscopy was also used as a safety measure to assess palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, and bulbar conjunctival injection at all study visits except the surgery visit (Day 0).

Dilated ophthalmoscopy

Dilated ophthalmoscopy assessment included evaluation of the optic nerve head for pallor and cupping (cup/disc ratio) and was performed at screening and on Day 15. For each subject, the investigator determined whether direct or indirect ophthalmoscopy should be used. Findings were recorded as normal or abnormal.

Use of rescue medication

At any time during the treatment period, any subject not responding adequately to the study treatment could be "rescued," or placed on alternate therapy, at the investigator's discretion. Any subject placed on rescue medication discontinued use of the study treatment and continued trial participation through the final visit (Day 17–19). Subjects who received rescue medication prior to Day 15 were considered treatment failures, but the need for rescue medication was not considered an AE. At some sites, anti-inflammatory medications were administered starting on Day 15 in the

absence of anterior chamber cells as standard-of-care, and this was not considered as a rescue.

Statistical analyses

The primary population for all efficacy analyses was the intent-to-treat (ITT) population, which was defined as all randomized subjects with at least one post-baseline (baseline = Day 1) evaluation. The safety population was defined as all subjects who received at least one dose of the allocated study treatment and from whom at least one safety assessment was obtained after randomization. Imputation for missing data was not applied.

Data from the efficacy and safety evaluations conducted during Trials 1 and 2 were analyzed separately and pooled, given the similarity in study design and purpose. The two vehicle groups in Trial 1 were pooled for all analyses of Trial 1 findings, because preliminary analyses illustrated no statistically significant differences between the two vehicle groups for the primary efficacy endpoints (complete resolution of anterior chamber cells at Day 8 maintained through Day 15 without rescue medication prior to Day 15 [$P=0.3130$]; complete resolution of ocular pain at Day 8 maintained through Day 15 without rescue medication prior to Day 15 [$P=0.6320$]). Because the purpose of the present research was to evaluate KPI-121 1% BID compared with vehicle, the results from the KPI-121 0.25% QID group from Trial 1 are not summarized here. For pooled efficacy analyses, all vehicle groups (Trial 1 QID, Trial 1 BID, and Trial 2 BID) were pooled; for pooled safety analyses the Trial 1 and Trial 2 BID vehicle groups were pooled but the Trial 1 vehicle QID group was excluded from the analyses.

Primary efficacy endpoints in both trials were evaluated using hierarchical statistical testing using the chi-squared statistic, with the provision that testing would cease if any single hypothesis had a P -value >0.05 . The primary endpoints were tested in the following sequence, comparing KPI-121 1% vs vehicle: 1) the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade =0) at postoperative Day 8 maintained through Day 15; 2) the difference in the proportion of study eyes with complete resolution of pain (grade =0) at postoperative Day 8 maintained through Day 15. Key non-primary endpoints were defined as the difference in the proportions of study eyes with: 1) complete resolution of anterior chamber cells (grade =0) at postoperative Day 15; 2) complete resolution of ocular pain (grade =0) at postoperative Day 4; and 3) complete resolution of ocular pain at postoperative Day 15. For each of these

primary and key non-primary endpoints, subjects treated with rescue medication prior to Day 15 were considered as nonresponders.

Separate and pooled summaries were created for all safety measures: evaluation of AEs, VA, IOP, slit-lamp biomicroscopy, dilated ophthalmoscopy, and use of rescue medication.

Results

Patient disposition and demographics

Across the two trials, 900 subjects were enrolled and included in the ITT populations: 380 subjects in Trial 1 and 520 subjects in Trial 2. Of these 900 subjects, 386 subjects were treated with KPI-121 1% BID, 125 subjects were treated with KPI-121 0.25% QID, 325 subjects were treated with vehicle BID, and 60 subjects were treated with vehicle QID. As illustrated in Table 1, there were no significant differences in the demographics of the enrolled populations between the two trials, and there were no significant differences among the treatment groups within each trial. Mean (range) ages were 67.7 (38–89) years for the pooled KPI-121 1% BID group (N=386) and 69.4 (40–90) years for the pooled vehicle group (N=385). Both trials, considered individually as well as pooled, enrolled more females than males, with a majority of subjects being White and not Hispanic/Latino.

Efficacy

Statistically significant between-group differences were observed for both primary efficacy endpoints, in both Trials (Table 2).

Pooled analyses of the two trials also demonstrated statistically significant results favoring KPI-121 1% over vehicle for each primary and key non-primary endpoint, as summarized in Table 3. Results for these endpoints are presented graphically in Figure 2 (for responders on anterior chamber cells at Days 8 and 15) and Figure 3 (for responders on ocular pain at Days 4, 8, and 15).

In Trial 1, complete resolution of anterior chamber cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 31.2% of subjects in the KPI-121 1% BID group, compared with 15.1% of subjects in the pooled vehicle group (between-group difference for percent responders: 16.1, 95% CI, 5.9–26.4, $P=0.0024$). Complete resolution of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 53.6% of subjects in the KPI-121 1% BID group, compared with 34.1% of subjects in the pooled vehicle group (between-group difference for percent responders: 19.5, 95% CI, 7.4–31.5, $P=0.0019$). Results for the key non-primary efficacy analysis were also significantly different favoring KPI-121 1% over vehicle for each analysis.

Table 1 Demographics and baseline characteristics (ITT population)

	Trial 1		Trial 2	
	KPI-121 1% BID (n=125)	Vehicle ^a (n=126)	KPI-121 1% BID (n=261)	Vehicle BID (n=259)
Age, years				
Mean	67.9	69.8	67.5	69.3
SD	9.4	7.3	8.67	8.52
Min, max	41, 89	52, 87	38, 89	40, 90
Gender, n (%)				
Male	50 (40.0)	48 (38.1)	117 (44.8)	115 (44.4)
Female	75 (60.0)	78 (61.9)	144 (55.2)	144 (55.6)
Ethnicity, n (%)				
Hispanic/Latino	15 (12.0)	13 (10.3)	38 (14.6)	36 (13.9)
Not Hispanic/Latino	110 (88.0)	113 (89.7)	223 (85.4)	223 (86.1)
Race, n (%)				
White	91 (72.8)	87 (69.0)	206 (78.9)	207 (79.9)
Asian	19 (15.2)	21 (16.7)	17 (6.5)	19 (7.3)
Black/African American	9 (7.2)	14 (11.1)	27 (10.3)	24 (9.3)
Other race	4 (3.2)	2 (1.6)	5 (1.9)	6 (2.3)
Native Hawaiian/other Pacific Islander	2 (1.6)	1 (0.8)	2 (0.8)	2 (0.8)
Mixed	0	1 (0.8)	2 (0.8)	0

Notes: ^aIn Trial 1, the two vehicle groups (vehicle A [QID] and vehicle B [BID]) were pooled for all analyses. For each trial, the ITT population was the primary population for all efficacy analyses.

Abbreviations: BID, twice daily; ITT, intent to treat; QID, four times daily.

Table 2 Summary of efficacy results for KPI-121 1% BID and vehicle groups by trial (ITT populations)

	Trial 1			Trial 2		
	KPI-121 1% BID (n=125)	Vehicle ^a (n=126)	P-value ^b	KPI-121 1% BID (n=261)	Vehicle BID (n=259)	P-value ^b
Primary endpoints, n (%)						
Complete resolution of anterior chamber cells at Day 8 maintained through Day 15 with no rescue medication prior to Day 15	39 (31.2)	19 (15.1)	0.0024	54 (20.7)	32 (12.4)	0.0105
Complete resolution of ocular pain at Day 8 maintained through Day 15 with no rescue medication prior to Day 15	67 (53.6)	43 (34.1)	0.0019	149 (57.1)	96 (37.1)	<0.0001
Key non-primary endpoints, n (%)						
Complete resolution of pain at Day 4 maintained through Day 15 with no rescue medication prior to Day 15	55 (44.0)	32 (25.4)	0.0020	109 (41.8)	64 (24.7)	<0.0001
Complete resolution of anterior chamber cells at Day 15 with no rescue medication prior to Day 15 ^c	68 (54.4)	38 (30.2)	0.0001	125 (47.9)	64 (24.7)	<0.0001
Complete resolution of pain at Day 15 with no rescue medication prior to Day 15 ^c	89 (71.2)	60 (47.6)	0.0001	179 (68.6)	126 (48.6)	<0.0001

Notes: ^aIn Trial 1, the two vehicle groups (vehicle A [QID] and vehicle B [BID]) were pooled for all analyses. ^bP-values are based on two-sided chi-squared tests, unadjusted, wherein the significance level was 0.05. ^cSubjects with missing scores at Day 15 were counted as nonresponders for the Day 15 analyses. Complete resolution = grade 0, for all scales. A subject was not considered to have been rescued if rescue medication started on the Day 15 visit date.

Abbreviations: BID, twice daily; ITT, intent to treat; QID, four times daily.

In Trial 2, complete resolution of anterior chamber cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 20.7% of subjects in the KPI-121 1% group, compared with 12.4% of subjects in the vehicle BID group (between-group difference for percent responders: 8.3, 95% CI, 2.0–14.7, $P=0.0105$). Complete resolution of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 57.1% of subjects in the KPI-121 1% group, compared with 37.1% of subjects in the vehicle BID group (between-group difference for percent responders: 20.0, 95% CI, 11.6–28.4, $P<0.0001$). Results for the key

non-primary efficacy analysis were also significantly different favoring KPI-121 1% over vehicle BID for each analysis in both trials (Table 2).

Safety AEs

In both Trial 1 and 2, considered individually and pooled, the incidence of AEs overall, treatment-related AEs, severe AEs, and AEs leading to discontinuation of treatment was lower in the KPI-121 1% BID group than the vehicle BID group (Tables 4 and 5). AEs were reported by 13.7% (53/386) and 17.5% (57/325) of subjects in the KPI-121 1% BID and

Table 3 Summary of efficacy results (pooled ITT populations)

	KPI-121 1% BID (n=386)	Vehicle ^a (n=385)	P-value ^b
Primary endpoints, n (%)			
Complete resolution of anterior chamber cells at Day 8 maintained through Day 15 with no rescue medication prior to Day 15	93 (24.1)	51 (13.2)	0.0001
Complete resolution of ocular pain at Day 8 maintained through Day 15 with no rescue medication prior to Day 15	216 (56.0)	139 (36.1)	<0.0001
Key non-primary endpoints, n (%)			
Complete resolution of pain at Day 4 maintained through Day 15 with no rescue medication prior to Day 15	164 (42.5)	96 (24.9)	<0.0001
Complete resolution of anterior chamber cells at Day 15 with no rescue medication prior to Day 15 ^c	193 (50.0)	102 (26.5)	<0.0001
Complete resolution of pain at Day 15 with no rescue medication prior to Day 15 ^c	268 (69.4)	186 (48.3)	<0.0001

Notes: ^aIn Trial 1, the two vehicle groups (vehicle A [QID] and vehicle B [BID]) were pooled for all analyses. This pooled vehicle group comprised both vehicle groups from Trial 1 and one vehicle group (dosed BID) in Trial 2. ^bP-values are based on two-sided chi-squared tests, unadjusted, wherein the significance level was 0.05. ^cSubjects with missing scores at Day 15 were counted as nonresponders for the Day 15 analyses. Complete resolution = grade 0, for all scales. A subject was not considered to have been rescued if rescue medication started on the Day 15 visit date.

Abbreviations: BID, twice daily; ITT, intent to treat; QID, four times daily.

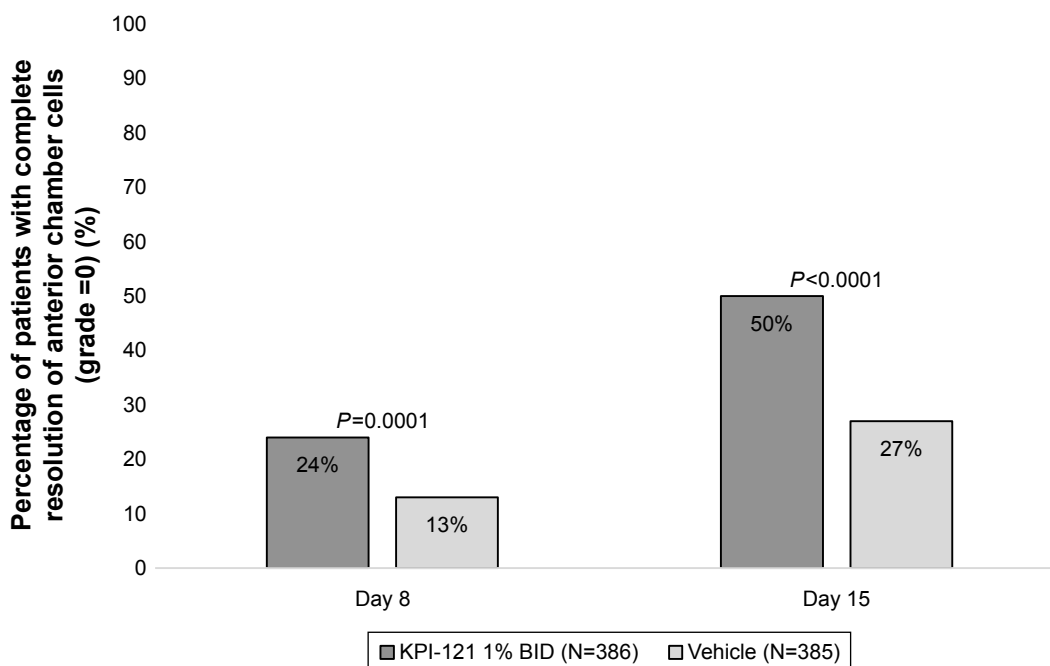


Figure 2 Proportions of subjects achieving and maintaining complete resolution of anterior chamber cells at Days 8 and 15 (pooled ITT population).

Notes: Data for the KPI-121 1% BID and vehicle treatment groups were pooled for both trials. Subjects were considered responders at Day X (ie, 8 or 15) if they had complete resolution of anterior chamber cells (grade =0) starting at that visit and continuing through Day 15 with no rescue medication prior to Day 15. A subject was not considered to have been rescued if rescue medication started on the Day 15 visit date. Subjects with missing scores at Day 15 were counted as nonresponders for the Day 15 analysis. P-values are based on two-sided chi-squared tests, unadjusted, wherein the significance level was $P=0.05$.

Abbreviations: BID, twice daily; ITT, intent to treat.

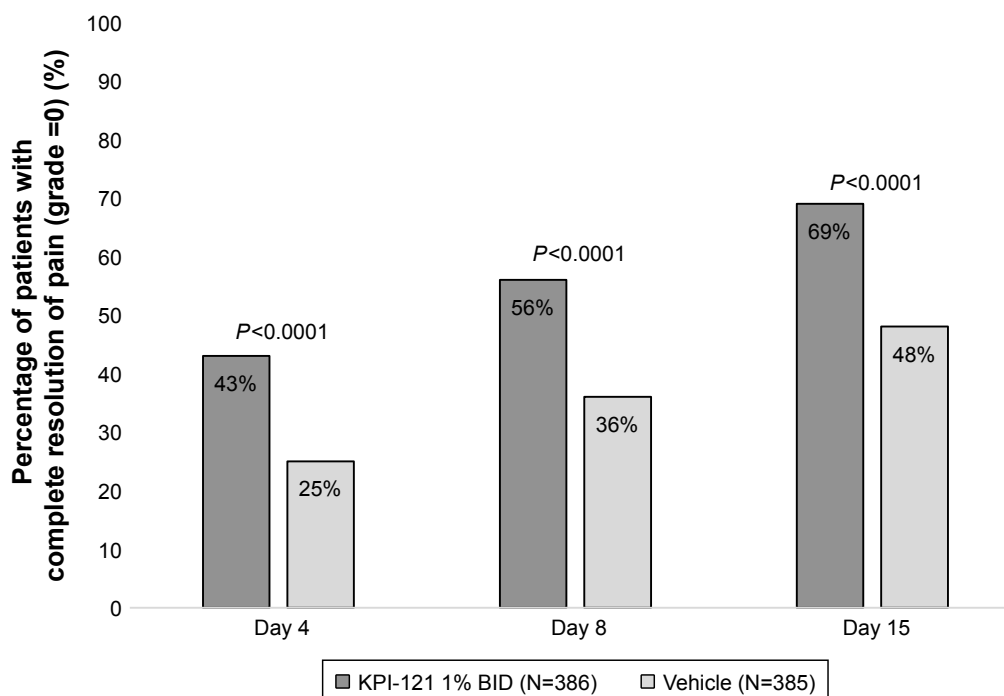


Figure 3 Proportions of subjects achieving and maintaining complete resolution of ocular pain at Days 4, 8, and 15 (pooled ITT population).

Notes: Data for the KPI-121 1% BID and vehicle treatment groups were pooled for both trials. Subjects were considered responders at Day X (ie, 4, 8, or 15) if they had complete resolution of ocular pain (grade =0) starting at that visit and continuing through Day 15 with no rescue medication prior to Day 15. A subject was not considered to have been rescued if rescue medication started on the Day 15 visit date. Subjects with missing scores at Day 15 (five subjects in the KPI-121 1% group and seven subjects in the vehicle group) were counted as nonresponders for the Day 15 analysis. P-values are based on two-sided chi-squared tests, unadjusted, wherein the significance level was $P=0.05$.

Abbreviations: BID, twice daily; ITT, intent to treat.

Table 4 Number (%) of subjects reporting AEs by category and trial (safety populations)

	Trial 1		Trial 2	
	KPI-121 1% BID (n=125)	Vehicle ^a (n=126)	KPI-121 1% BID (n=261)	Vehicle BID (n=259)
Any AEs	15 (12.0)	26 (20.6)	38 (14.6)	42 (16.2)
AEs related to treatment ^b	1 (0.8)	9 (7.1)	9 (3.4)	7 (2.7)
Severe study eye AEs ^c	0	3 (2.4)	2 (0.8)	2 (0.8)
Serious AEs	1 (0.8)	2 (1.6)	1 (0.4)	2 (0.8)
AEs that led to discontinuation of treatment	2 (1.6)	12 (9.5)	5 (1.9)	10 (3.9)

Notes: ^aIn Trial 1, the two vehicle groups (vehicle A [QID] and vehicle B [BID]) were pooled for all analyses. ^bSubjects reporting the same AE in more than one relationship category were counted in the greatest relationship category. ^cSubjects reporting one or more AEs were counted once at the maximum intensity of all AEs.

Abbreviations: AE, adverse event; BID, twice daily; QID, four times daily.

vehicle BID groups, respectively. Most AEs were of mild or moderate severity. The most commonly reported ($\geq 1\%$ in any treatment group) preferred terms were eye pain, headache, photophobia, posterior capsule opacification, corneal edema, and nasopharyngitis (Tables 6 and 7).

VA

In both Trial 1 and Trial 2, a review of Snellen distance VA data revealed no clinically important differences between the KPI-121 1% BID group and the vehicle group in terms of mean changes from baseline in VA at any post-baseline assessment. Pooled summaries illustrated that changes from baseline in VA were negligible in both the KPI-121 1% BID and vehicle groups.

IOP

In Trial 1 and Trial 2, as well as in the pooled analysis of both trials, mean IOP measurements of study eyes at each scheduled visit as well as increased IOP were similar across treatment groups (Table 8). Additionally, IOP elevations of ≥ 10 mmHg compared with baseline and a raw IOP measurement of ≥ 21 mmHg in the study eye were experienced by 0.5% (2/386) and 0% (0/325) of subjects in the KPI-121 1% BID and vehicle BID groups, respectively. Using a very strict definition of IOP elevation, ≥ 5 mmHg increase and a

raw IOP measurement of ≥ 21 mmHg in the study eye, again both groups experienced similar incidence, 1.3% (5/386) and 0.6% (3/325) in the KPI-121 1% BID and vehicle groups, respectively. These results indicate that no unexpected safety signal was observed relative to IOP following KPI-121 1% treatment.

Slit-lamp biomicroscopy

In Trial 1 and Trial 2, as well as in the pooled analysis of both trials, no clinically important differences were observed based on safety evaluations of slit-lamp biomicroscopy (palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, and bulbar conjunctival injection) between the KPI-121 1% BID and vehicle groups, and no significant differences from baseline were observed in either group.

Dilated ophthalmoscopy

In Trial 1 and Trial 2, as well as in the pooled analysis of both trials, no clinically important differences between the KPI-121 1% BID and vehicle groups were observed based on evaluations from dilated ophthalmoscopy. There was a low prevalence of abnormal disc pallor and similar cup/disc ratio scores at both screening and Day 15 for KPI-121 1% BID and vehicle groups.

Table 5 Number (%) of subjects reporting AEs by category (pooled safety population)

	KPI-121 1% BID (n=386)	Vehicle BID (n=325)
Any AEs	53 (13.7)	57 (17.5)
AEs in the study eye	28 (7.3)	42 (12.9)
AEs related to treatment ^a	10 (2.6)	12 (3.7)
Severe AEs ^b	4 (1.0)	7 (2.2)
Serious AEs	2 (0.5)	2 (0.6)
AEs that led to discontinuation of treatment	7 (1.8)	17 (5.2)

Notes: ^aSubjects reporting the same AE in more than one relationship category were counted in the greatest relationship category. ^bSubjects reporting one or more AEs were counted once at the maximum intensity of all AEs.

Abbreviations: AE, adverse event; BID, twice daily.

Table 6 Number (%) of subjects reporting common ($\geq 1\%$ in either group) AEs by trial (safety populations)

	Trial 1		Trial 2	
	KPI-121 1% BID (n=125)	Vehicle ^a (n=126)	KPI-121 1% BID (n=261)	Vehicle BID (n=259)
Headache	2 (1.6)	3 (2.4)	4 (1.5)	4 (1.5)
Corneal edema	2 (1.6)	2 (1.6)	0	0
Eye pain	1 (0.8)	5 (4.0)	3 (1.1)	6 (2.3)
Photophobia	1 (0.8)	3 (2.4)	1 (0.4)	4 (1.5)
Eye irritation	1 (0.8)	3 (2.4)	0	0
Nasopharyngitis	0	0	4 (1.5)	1 (0.4)
Posterior capsule opacification	0	0	3 (1.1)	4 (1.5)
Cystoid macular edema	0	0	3 (1.1)	3 (1.2)
Instillation site pain	0	0	1 (0.4)	2 (1.2)
Ocular hyperemia	0	5 (4.0)	0	0
Eye inflammation	0	4 (3.2)	0	0
Ocular discomfort	0	2 (1.6)	0	0

Notes: ^aIn Trial 1, the two vehicle groups (vehicle A [QID] and vehicle B [BID]) were pooled for all analyses. MedDRA version 16.1 was used to code all AEs in each trial. Preferred terms are listed in descending order of incidence for the KPI-121 1% BID group in Trial 1 and then the KPI-121 1% BID group in Trial 2.

Abbreviations: AE, adverse event; BID, twice daily; QID, four times daily.

Use of rescue medication

Rescue medication was used at any time prior to Day 15 in Trial 1 by 14 patients (11.2%) in the KPI-121 1% group vs 48 patients (38.1%) in the vehicle group, and in Trial 2 by 45 patients (17.2%) in the KPI-121 1% group vs 96 patients (37.1%) in the vehicle group.

Discussion

Results from two double-masked, randomized, vehicle-controlled trials provide evidence of the efficacy of KPI-121 1% ophthalmic suspension administered twice daily for 2 weeks in the resolution of anterior chamber cells and ocular pain following cataract surgery. In both trials, a significantly greater proportion of subjects treated with KPI-121 1% BID compared to vehicle demonstrated a response to treatment, in terms of complete resolution of anterior chamber cells (ie, grade =0) at Days 8 and 15 (each maintained through Day 15 without use of rescue medication) and complete clearing (ie, grade =0) of ocular pain at Days 4, 8, and 15 (each maintained

through Day 15 without use of rescue medication). Additionally, summaries of safety measures, including AEs, VA, IOP, slit-lamp biomicroscopy, dilated ophthalmoscopy, and use of rescue medication, demonstrated that KPI-121 1% BID was also found to be safe and well tolerated with no new or unexpected safety concerns observed during the trial.

The AE profile was composed primarily of events that were local to the site of treatment, mild in severity, reversible, and nonserious, and most reported preferred terms were consistent with those that would be expected in a population that had recently undergone routine, uncomplicated cataract surgery and received topical ophthalmic corticosteroid treatment. AEs recognized as common with corticosteroid use were reported with low incidence in the KPI-121 1% group. In the pooled analysis of AEs, the incidence of AEs was lower in the KPI-121 1% group than in the vehicle group for all AEs overall, treatment-related AEs, severe AEs, and AEs leading to discontinuation of treatment.

As demonstrated in these two studies, KPI-121 1% with MPP technology delivers a desirable combination of robust efficacy with twice daily dosing, a low overall incidence of AEs, and the favorable IOP-safety profile consistently demonstrated with LE.⁸⁻¹⁴ While the efficacy and safety of LE in treating postoperative inflammation and pain are well established,¹⁵⁻²² all currently available formulations require QID dosing. This is due at least in part to the eye's innate ability to remove foreign material, including suspended drug particles, from the ocular surface. One of the key mechanisms of this removal involves mucin, the primary component of mucus, which provides a key protective role for the ocular surface. The cornea and conjunctiva are covered with a 3- to

Table 7 Number (%) of subjects reporting common ($\geq 1\%$ in either group) AEs (pooled safety population)

	KPI-121 1% BID (n=386)	Vehicle BID (n=325)
Headache	6 (1.6)	6 (1.8)
Eye pain	4 (1.0)	9 (2.8)
Posterior capsule opacification	4 (1.0)	4 (1.2)
Nasopharyngitis	4 (1.0)	1 (0.3)
Photophobia	2 (0.5)	6 (1.8)
Corneal edema	2 (0.5)	4 (1.2)

Notes: MedDRA version 16.1 was used to code all AEs in each trial. Preferred terms are listed in descending order of incidence for the KPI-121 1% BID group.

Abbreviations: AE, adverse event; BID, twice daily.

Table 8 Summary of assessments of intraocular pressure in study eyes (pooled safety population)

	KPI-121 1% BID (n=386)	Vehicle BID (n=325)
Intraocular pressure (mmHg), n (%)		
>5 mmHg increase from baseline	19 (4.9)	8 (2.5) ^a
>5 mmHg increase from baseline + ≥21 mmHg measurement	5 (1.3)	3 (0.6) ^a
≥10 mmHg increase from baseline	3 (0.8)	0 ^a
≥10 mmHg increase from baseline + ≥21 mmHg measurement	2 (0.5)	0 ^a

Notes: ^an=320; five subjects in the pooled vehicle group did not have any post-baseline IOP measurement.

Abbreviation: BID, twice daily.

40- μ m layer of mucus.^{7,23–25} The outer layer of secreted and other mucins primarily traps and rapidly eliminates allergens, pathogens, and other particles (eg, corticosteroids in eye drops) while the cell-bound mucins of the inner glycocalyx protect the cornea from abrasive stress and turn over much less rapidly.^{7,26} The ability to penetrate the outer mucin matrix and reach the glycocalyx will likely increase the penetration and retention of drug particles on the ocular surface and enhance drug release to the underlying tissues.⁷ In order to penetrate the mucin meshwork effectively, particles must be sufficiently small in size (<500 nm) and have the ability to overcome the adhesive nature of the ocular mucus layer.^{27,28}

MPP technology uses proprietary methods to create a novel nanoparticle formulation of LE designed to evade these mucus barriers. Coarse drug particles are milled in the presence of an MPP enabling surface-altering agent until the particle size is reduced to ~200–400 nm. In an ocular pharmacokinetic study in rabbits, a 0.4% suspension of LE-MPP produced peak concentrations approximately three-fold higher in ocular tissues (cornea, conjunctiva, iris/ciliary body, retina) and aqueous humor compared to Lotemax[®] suspension.⁷

KPI-121 1% is a novel suspension of MPP-coated LE nanoparticles formulated with excipients approved by FDA for ophthalmic use.⁷ LE was selected for the formulation based upon several criteria including high lipophilicity, high binding affinity for the glucocorticoid receptor, and extensive and predictable metabolism to inactive metabolites by tissue esterases.²⁹

Conclusion

KPI-121 1% given BID was effective in resolving postoperative inflammation and pain following cataract surgery, based on analyses demonstrating statistical significance compared with vehicle on the primary and key non-primary efficacy endpoints of pain and inflammation. It was safe and well tolerated with no new or unexpected safety concerns observed during the trials. KPI-121 1% offers clinicians an efficacious

BID treatment option for inflammation and pain after ocular surgery which provides significant benefit to patients while retaining the favorable safety profile of loteprednol.

Disclosure

This study was sponsored and funded by Kala Pharmaceuticals, Inc, which participated in the design of the study and oversaw its conduct, monitoring, and analysis. Dr Kim, Dr Sall, Dr Holland, and Dr Gupta are consultants for Kala Pharmaceuticals, Inc. Dr Brazzell and Dr Coultas are employees of Kala Pharmaceuticals, Inc. The abstract of this paper was presented at the 2018 American Society of Cataract and Refractive Surgery (ASCRS) Annual Meeting as a paper presentation with interim findings. The paper's abstract was published in the "Paper Session Abstracts" on the ASCRS conference website: <https://ascrs.confex.com/ascrs/18am/meetingapp.cgi/Paper/47263>.

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Supplementary materials

Table S1 List and description of investigators, who enrolled at least one subject in the study, and other important participants in KPI-121 1% Trial I

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Ranjan P Malhotra, MD, FACS	Gregg J Berdy, MD, FACS Robert C Brusatti, OD	Ophthalmology Associates, 12990 Manchester Road, Suite 200, St Louis, MO 63131, USA
Robert DaVanzo, MD	Michael Emile Tepedino, MD James Zachary Forsey, MD	Cornerstone Eye Care, 1400 East Hartley Drive, High Point, NC 27262, USA
Alice Epitropoulos, MD		Ophthalmic Surgeons & Consultants of Ohio, 262 Neil Avenue, Suite 430, Columbus, OH 43215, USA
Raymond Fong, MD	Jeffrey C Paccione, MD Douglas B Friedrich, MD Jason J Chen, OD	Raymond Fong, MDPC, 109 Lafayette Street, 4th floor, New York, NY 10013, USA
Joseph Gira, MD	Micheal Donahoe, MD Erin Sullivan, OD Michelle Derhelmer, MD	Ophthalmology Consultants Ltd, 12990 Manchester Road, Suite 201, St Louis, MO 63131, USA
Damien Goldberg, MD	Barry Wolstan, MD	Wolstan & Goldberg Eye Associates, 23600 Telo Avenue, Suite 100, Torrance, CA 90505, USA
Paul J Hartman, MD	Alan H Gruber, MD Howard I Schenker, MD	Rochester Ophthalmological Group, PC, 2100 South Clinton Avenue, Rochester, NY 14618, USA
Farrell Tyson, MD	Michael Tibbitts, MD Stewart Kaplan, OD	Argus Research at Cape Coral Eye Center, 4120 Del Prado Boulevard S, Cape Coral, FL 33904, USA
Douglas Lorenz, DO	Mark Stradling, DO Surjeet Singh, MD Rene Zamora, MD Darrick Neibaur, DO Vincent Gassen, OD Douglas Orton, OD Rajy Rouweyha, MD	Nevada Eye and Ear, 2598 Windmill Parkway, Henderson, NV 89074, USA Las Vegas Physicians Research Group, 870 Seven Hills Drive, Suite 201, Henderson, NV 89052, USA Seven Hills Surgical Center, 876 Seven Hills Drive, Henderson, NV 89052, USA Stone Creek Surgical Center, 5915 S Rainbow Boulevard, Las Vegas, NV 89118, USA
Joseph Martel, MD	James Martel, MD	Martel Eye Medical Group, 11216 Trinity River Drive, Rancho Cordova, CA 95670, USA Martel Eye Institute, LLC, 11216 Trinity River Drive, Rancho Cordova, CA 95670, USA Mercy San Juan Surgery Center, 6660 Coyle Avenue, Carmichael, CA 95608, USA

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Table S1 (Continued)

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Bernard Milstein, MD	Da-Thuy Van, DO	The Eye Clinic of Texas, Affiliate of Houston Eye Associates, 1100 Gulf Freeway, Suite 114, League City, TX 77573, USA Area Surgicare Center, 502 Medical Center Boulevard, Webster, TX 77598, USA
Sebastian Mora, MD	John Kozlovsky, MD Jeannie Camacho, OD	Kozlovsky Delay & Winter Eye Consultants, LLC, 2929 Mossrock, Suite 104, San Antonio, TX 78230, USA
Michael Nordland, MD, PhD		Cincinnati Eye Institute, 1945 CEI Drive, Cincinnati, OH 45242, USA Cincinnati Eye Institute, 4701 Central Avenue, Middletown, OH 45044, USA
Francis Price, MD	Yuri McKee, MD Mathew Feng, MD Kathleen Kelley, OD Faye Peters, OD	Price Vision Group, 9002 North Meridian Street, Suite 100, Indianapolis, IN 46260, USA
Charles Reilly, MD	William Flynn, MD Edward Rashid, MD Robert Rice, MD	R and R Eye Research, LLC, 5430 Fredericksburg Road, Suite 100, San Antonio, TX 78229, USA Specialty Surgery Center, 5255 Prue Road, Suite 100, San Antonio, TX 78240, USA
Lawrence Roel, MD	Richard M Francis, MD	Westside Research, LLC, 1413 John B White Sr Boulevard, Spartanburg, SC 29306, USA
Kenneth Sall, MD		Sall Research Medical Center, 11423 187th Street, Suite 200, Artesia, CA 90701, USA
John Sheppard, MD	Walter O Whitley, OD Elizabeth Yeu Lin, MD Dayna Lago, MD Stephen Scoper, MD	Virginia Eye Consultants, 241 Corporate Boulevard, Norfolk, VA 23502, USA
Robert J Smyth-Medina, MD	Steven Rauchman, MD	North Valley Eye, 11550 Indian Hills Road, Suite 341, Mission Hills, CA 91345, USA
Joseph Tauber, MD	No sub-investigator	Tauber Eye Center, 4400 Broadway, Suite 202, Kansas City, MO 64111, USA
Lloyd Taustine, MD	Gregory M Sulkowski, MD Brian K Kritchman, MD James D Hurt, OD	Taustine Eye Center, 1169 Eastern Parkway, Suite 3427, Louisville, KY 40217, USA
Navin Tekwani, MD		Tekwani Vision Center, 9911 Kennerly Road, Suite A, St Louis, MO 63128, USA
Steve Wilson, OD	Timothy Schmitt, MD	John-Kenyon, 519 State Street, New Albany, IN 47150, USA
Harvey DuBiner, MD	Ronald Weber, MD Joon Y Kim, MD Carey Jenkins, MD Heather Ambrosia, MD Kimberley Betton, OD	Eye Care Centers Management, Inc (Clayton Eye Center), 1000 Corporate Center Drive, Suite 100, 120, 180, Morrow, GA 30260, USA

Table S2 List and description of investigators, who enrolled at least one subject in the study, and other important participants in KPI-121 1% Trial 2

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Joseph R Martel, MD	James Benjamin Martel, MD, MPH	Martel Eye Medical Group, 11216 Trinity River Drive, Rancho Cordova, CA 95670, USA
Kenneth Sall, MD	Julie Kim, OD Jade Davis, OD	Sall Research Medical Center, 11423 187th Street, Suite 200, Artesia, CA 90701, USA
Michael Korenfeld, MD	Nathan Tuttle, OD	Comprehensive Eye Care, Ltd, 901 East Third Street, Washington, MO 63090, USA Mercy Hospital, 901 East Fifth Street, Washington, MO 63090, USA
Jack Abrams, MD	Tapan R Shah, MD	Abrams Eye Institute, 6450 Medical Center Street, Suite 100, Las Vegas, NV 89148, USA Valley View Surgery Center, 1330 S Valley View Boulevard, Las Vegas, NV 89102, USA
Louis M Alpern, MD		The Cataract and Glaucoma Center, 4171 N Mesa, Building D100, El Paso, TX 79902, USA
Jason Bacharach, MD	Lisa Teel, OD	North Bay Eye Associates, 104 Lynch Creek Way, Suite 12, Petaluma, CA 94954, USA North Bay Eye Associates, Inc, Ambulatory Surgery Center, 380 Tesconi Court, Santa Rosa, CA 95401, USA
Mark T Bergmann, MD	Daniel J Hammer, MD	Apex Eye, 6507 Harrison Avenue, Suite E, Cincinnati, OH 45247, USA Trihealth Surgery Center, 3660 Edgewood Drive, Cincinnati, OH 45211, USA Mercy Health West Hospital, 3300 Mercy Health Boulevard, Cincinnati, OH 45211, USA
James Boyce, MD	Norman Liu, MD Ryan Taban, MD	Orange County Ophthalmology, 12665 Garden Grove, Boulevard, Suite 401, Garden Grove, CA 92843, USA
David L Cooke, MD	David N Brown, MD Ronald L McKey, MD Stanley W Pletcher, MD Duane A Tolsma, OD	Great Lakes Eye Care, 2848 Niles Road, Saint Joseph, MI 49085, USA Great Lakes Eye Care, 120 Longmeadow Village, Drive Niles, MI 49120, USA Lakeland Center for Outpatient Services, 3900 Hollywood Road, Saint Joseph, MI 49085, USA

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Table S2 (Continued)

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Michael Deppenbusch, MD	Anita Schadlu, MD Ramin Schadlu, MD Shabari Seetharam, MD	Arizona Eye Center, 604 W Warner Road, Suite B6, Chandler, AZ 85225, USA Warner Park Surgery Center, 604 W Warner Road, Building A, Chandler, AZ 85225, USA Scottsdale Eye Institute, 215 S Power Road, Suite 112, Mesa, AZ 85206, USA Desert Ridge Outpatient Surgery Center, 20940 N Tatum Boulevard, # 100, Phoenix, AZ 85050, USA
Sherif M El-Harazi, MD	Kay Park, MD	Lugene Eye Institute, 1510 South Central Avenue, Suite 300, Glendale, CA 91204, USA
Robert H Gross, MD	Jung T Dao, MD Brandon K Suedekum, MD	Cornea and Cataract Consultants of Arizona, 3815 E Bell Road, Suite 2500, Phoenix, AZ 85032, USA
Preeya Gupta, MD	Terry Kim, MD Melissa Daluvoy, MD Gargi Vora, MD Robin R Vann, MD	Duke University Eye Center, 2351 Erwin Road, Durham, NC 27710, USA Duke Eye Center, 4709 Creekstone Drive, Durham, NC 27703, USA
David Hardten, MD	Ahmad Fahmy, OD Christine Larson, MD Elizabeth Davis, MD Gina Doeden, OD Johnna Hobbs, OD Mona Fahmy, OD Mark Bubolz, OD Scott Hauswirth, OD Thomas Samuelson, MD Alicia Alvarado, OD	Minnesota Eye Consultants, PA, 9801 Dupont Avenue S, Suite 200, Bloomington, MN 55431, USA
Mitchell A Jackson, MD		Jackson Eye, SC, 300 N Milwaukee Avenue, Lake Villa, IL 60046, USA Lindenhurst Surgery Center, 1050 Red Oak Lane, Lindenhurst, IL 60046, USA
Brennan P Greene, MD	John C Meyer, MD Guruprasad R Pattar, MD, PhD	The Eye Care Institute, 1536 Story Avenue, Louisville, KY 40206, USA
Karl Olsen, MD	Kent Basford, DO Randall Smith, MD	Eye Center of Northern Colorado, PC, 1725 East Prospect Road, Fort Collins, CO 80525, USA

(Continued)

Table S2 (Continued)

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Richard J Ou, MD	John M Lim, MD	Houston Eye Associates, 915 Gessner #250, Professional building 3, Houston, TX 77024, USA Houston Eye Associates, 2855 Gramercy Street, Houston, TX 77025, USA
James H Peace, MD		United Medical Research Institute, 431–433 North Prairie Avenue, Inglewood, CA 90301, USA Olympia Medical Center, 5900 West Olympic Boulevard, Los Angeles, CA 90036, USA
Harvey J Reiser, MD	Carrie A Cardillo, OD	Eye Care Specialists, 703 Rutter Avenue, Kingston, PA 18704, USA Surgical Specialty Center of Northeastern Pennsylvania, 190 Welles Street, Forty Fort, PA 18704, USA
Philip Lee Shettle, DO	None	Shettle Eye Research, Inc, 13113 66th Street N, Largo, FL 33773, USA
Bruce E Silverstein, MD	Christopher Lin, MD Robert G Trent, MD Bryan G Crum, MD	Shasta Eye Medical Group, Inc, 3190 Churn Creek Road, Redding, CA 96002, USA Shasta Eye Medical Group, Inc, 900 Butte Street, Redding, CA 96001, USA Surgery Center of Northern California, 950 Butte Street, Redding, CA 96001, USA
Steven E Smith, MD	Angela Kaplan, OD	Eye Associates of Fort Myers, 4225 Evans Avenue, Fort Myers, FL 33901, USA University Eye Surgery Center, 13051 University Drive, Fort Myers, FL 33907, USA
Thomas Richard Walters, MD	Robert Edward Marquis, MD Yen Dang Nieman, MD	Texan Eye, PA/Keystone Research, Ltd, 5717 Balcones Drive, Austin, TX 78731, USA Texan Eye, PA, 7000 North Mopac Expressway, Suite 110 and Suite 165, Austin, TX 78731, USA Texan Surgery Center, 7000 North Mopac Expressway, Suite 120, Austin, TX 78731, USA

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Table S2 (Continued)

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Jon-Marc Weston, MD, FACS	Gregory M Valle, OD Steven F Tronnes, OD	Roseburg Research Associates, LLC, 2435 NW Kline Street, Roseburg, OR 97471, USA Vision Surgery & Laser Center, PC, 2435 NW Kline Street, Roseburg, OR 97471, USA
Robert B Pendleton, MD	Victor Wechter, MD	Pendleton Eye Center, 3637 Vista Way, Oceanside, CA 92056, USA North Coast Surgery Center, 3903 Waring Road, Oceanside, CA 92056, USA
John F Kozlovsky, MD	Jeannine E Camacho, OD Richard L Delay, OD	Kozlovsky Delay & Winter Eye Consultants, LLC, 2929 Mossrock, Suite 104, San Antonio, TX 78230, USA American Surgery Center, 7810 Louis Pasteur Drive, Suite 100, San Antonio, TX 78229, USA
Parag Majmudar, MD	Maria Rosselson, MD Tiffany Andrzejewski, OD Charles Faron, OD	Chicago Cornea Consultants, 1585 N Barrington Road, Suite 502, Hoffman Estates, IL 60169, USA St Alexius Medical Center, 1555 N Barrington Road, Hoffman Estates, IL 60169, USA Hoffman Estates Surgery Center, 1555 N Barrington Road, Suite 400, Hoffman Estates, IL 60169, USA
Jeffrey Raymond Lozier, MD	Karen Mossbarger, CRC	Arch Health Partners, 15611 Pomerado Road, 4th Floor, Poway, CA 92064, USA
Kerry D Solomon, MD	Jeffery F Hood, OD Helga P Sandoval, MD, MSCR	Carolina Eye Care Physicians, LLC, 1101 Clarity Road, Suite 100, Mt Pleasant, SC 29464, USA The Physicians' Eye Surgery Center, 2060 Charlie Hall Boulevard, Suite 301, Charleston, SC 29464, USA
David Tyler Vroman, MD	Millin Chandu Budev, MD Michelle See Yuen Ying, MD Kristina D Neff, MD	Carolina Cataract & Laser Center, 137 Gateway Drive, Ladson, SC 29456, USA Physicians Eye Surgery Center, 2060 Charlie Hall Boulevard, Suite 301, Charleston, SC 29414, USA
Don J Perez-Ortiz, MD	Bernard R Perez, MD	International Research Center, 4506 Wishart Place, Tampa, FL 33603, USA

(Continued)

Table S2 (Continued)

Investigator name	Sub-investigator(s) name	Hospital/institution name and address
Thomas LoBue, MD	Ryan Miller, OD	LoBue Laser and Eye Medical Center, 40700 California Oaks Road, Suite 106, Murrieta, CA 92562, USA
Frank Wilson McDonald, MD	Jeffery Levenson, MD Curtis Schmidt, OD	Levenson Eye Associates, 751 Oak Street, Suite 200, Jacksonville, FL 32204, USA Riverside Park Surgicenter, 2001 College Street, Jacksonville, FL 32204, USA
Robert C Sorenson, MD, PhD	Barratt L Philips, MD Roger Duncan Johnson, MD John Grant Tew, MD	Inland Eye Specialist, 3953 W Stetson Avenue, Hemet, CA 92545, USA

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