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APPLICATION NUMBER:

210933Orig1s000

CLINICAL REVIEW(S)

Clinical Review
William M. Boyd, M.D.
NDA 210933 Class 2 resubmission
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

CLINICAL REVIEW of NDA 210933
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%
Class 2 Resubmission

Application Type	NDA
Application Number(s)	210933
Priority or Standard	Standard
Submit Date(s)	April 30, 2020
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PDUFA Goal Date	October 30, 2020
Division/Office	OND/DO
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	October 22, 2020
Established/Proper Name	loteprednol etabonate ophthalmic suspension, 0.25%
(Proposed) Trade Name	EYSUVIS
Applicant	Kala Pharmaceuticals, Inc.
Dosage Form(s)	ophthalmic suspension
Proposed Dosing Regimen(s)	Instill one to two drops into each eye four times daily for two weeks
Proposed Indication	for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease
Recommendation on Regulatory Action	Recommend Approval

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert

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PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
TEAE	treatment emergent adverse event

1. 1. Executive Summary

1.1. Product Introduction

This is a 505(b)(2) new drug application for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%. The reference listed drug is LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, NDA 020583. The Applicant's bridge consists of chemical identity, and comparative nonclinical pharmacokinetics (PK). In this review, EYSUVIS may also be referred to as KPI-121 0.25%.

On August 7, 2019, Kala received a complete response letter (CRL) from the Agency, in which the following was communicated: "It is recommended that to demonstrate substantial evidence of efficacy in the intended patient population, data from at least one additional clinical trial be submitted in which loteprednol etabonate ophthalmic suspension, 0.25% demonstrates superiority to its vehicle in the treatment of signs and symptoms of dry eye disease." The results from an additional Phase 3 trial (STRIDE 3; KPI-121-C-011) are included in this Class 2 resubmission for the application.

Loteprednol etabonate is a corticosteroid. Corticosteroids have been shown to inhibit the inflammatory response to a variety of inciting agents. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms.

Ocular AEs generally associated with ophthalmic steroids include elevated intraocular pressure (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis. Topical ophthalmic corticosteroid products are approved for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies. Kala believes a significant unmet need exists for a safe

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and effective corticosteroid product to provide reliable temporary relief of the signs and symptoms of dry eye. The applicant has proposed a two-week dosing to potentially address the known ocular adverse event profile of corticosteroids. Topical ophthalmic corticosteroid products have a class a Warning about the need for additional monitoring, if the product is used for more than 10 days.

1.2. **Conclusions on the Substantial Evidence of Effectiveness and Safety**

BLA 210933, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, is recommended for approval. The clinical trials submitted in this application support an indication for the temporary relief from the signs and symptoms of dry eye disease. The potential serious adverse events associated with the use of topical ophthalmic corticosteroids can be minimized with requirements for slit lamp examinations prior to prescribing and with limitations on dosing for no more than 2 weeks.

1.3. **Benefit-Risk Assessment**

Studies -002, -006, -007 and -011 demonstrated superiority of EYSUVIS to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15. Studies -006 and -011 demonstrated superiority of EYSUVIS to the vehicle for the primary symptom endpoint. The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of EYSUVIS for two weeks can be monitored with slit lamp and fundus examinations. The clinical benefits of short term use outweigh the recognized steroid class concerns when prescribed after appropriate slit lamp evaluation.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	The health and function of the cornea is dependent on a thin tear film layer made up of an aqueous, mucin, lipids, lysozymes, immunoglobulins, glucose, and salts. In keratoconjunctivitis sicca (dry eye), one or more of the components is deficient.	Keratoconjunctivitis sicca (dry eye) is a potentially debilitating condition which can impede the activities of daily living and can be associated with anterior segment damage to the eye.
<u>Current Treatment Options</u>	Currently available treatments for keratoconjunctivitis sicca (dry eye) include the use of OTC demulcents, Rx topical calcineurin inhibitors (cyclosporine ophthalmic emulsion and cyclosporine ophthalmic solution), and/or a topical lymphocyte function-associated antigen-1 (LFA-1) antagonist (lifitegrast ophthalmic solution).	This product would provide an alternative product to temporarily treat the signs and symptoms of dry eye disease.
<u>Benefit</u>	Four studies demonstrated superiority of EYSUVIUS to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15, two of these studies demonstrated superiority of EYSUVIS to the vehicle for the primary symptom endpoint.	EYSUVIUS has demonstrated the improvement in the signs and symptoms of dry eye with a short course of treatment.
<u>Risk and Risk Management</u>	Serious adverse reactions associated with ophthalmic corticosteroids include elevated IOP, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.	The potential serious adverse events associated with the use of topical ophthalmic corticosteroids can be managed with limitations on dosing for two weeks and monitoring with slit lamp examinations.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Section 6.1
☒	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Keratoconjunctivitis sicca (KCS), commonly referred to as dry eye, is a disease affecting the ocular surface, the tear film, and related ocular tissues and organs. The ocular surface is supported and maintained by the tear film, which is composed of 3 distinct components (lipid, aqueous, and mucin) that make up 2 fluid layers. Meibomian glands along the upper and lower lid margins produce the outer lipid layer of the tear film. The inner layer, an aqueous and mucin mixture, is composed of aqueous fluid produced by the main and accessory lacrimal glands and mucins produced by goblet cells on the conjunctival epithelium as well as corneal epithelial cells.

Signs of dry eye include, but are not limited to, corneal staining, conjunctival staining, decreased tear breakup time, decreased Schirmer's tear test with or without anesthesia. Symptoms of dry eye include, but are not limited to, blurred vision, light sensitivity, sandy/gritty feeling, ocular irritation, ocular pain or discomfort, and ocular itching.

Safety and efficacy for the treatment of dry eye disease indication is recommended to be demonstrated in adequate and well-controlled, independent trials. A demonstration of a statistically significant difference between the test treatment and vehicle for at least one objective sign and at least one subjective symptom of dry eye is expected. Clearing of corneal staining is also considered clinically relevant. Increases of ≥ 10 mm in Schirmer wetting from baseline have been validated (i.e. qualified) as being clinically relevant based on correlation with decreased corneal staining.

2.2. Analysis of Current Treatment Options

Table 1 - FDA Approved Treatments

Indication:	To increase tear production	
Restasis	cyclosporine ophthalmic emulsion	NDA 50790
Cequa	cyclosporine ophthalmic solution	NDA 210913
Indication:	To treat signs and symptoms of dry eye disease	
Xiidra	lifitegrast ophthalmic solution	NDA 208073

Current management of dry eye disease often begins with artificial tear replacement and other palliative treatments such as punctal occlusion.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Loteprednol etabonate (LE) is a corticosteroid that was originally developed as a topical ophthalmic suspension 0.5% [LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, NDA 020583]. LOTEMAX is approved for the treatment of steroid responsive inflammatory conditions when the inherent hazard of steroid use is accepted to obtain an advisable diminution of edema and inflammation and for the treatment of postoperative inflammation following ocular surgery.

3.2. Summary of Presubmission/Submission Regulatory Activity

A Pre-IND (IND 17192) meeting was held between the sponsor and the FDA on April 4, 2013.

A Type C, End of Phase 2 meeting was held on May 3, 2016.

A CMC pre-NDA meeting was held on May 12, 2017.

A Type B Pre-NDA meeting was held on August 16, 2017. The purpose of the meeting was to discuss the statistical analysis plan for the ongoing Phase 3 trials and format and content of the nonclinical and clinical modules of the upcoming NOA submission.

A Type C Guidance meeting was held on May 8, 2018, to discuss the results of their Phase 2 and Phase 3 clinical trials for KPI-121 0.25% and whether their product has sufficient safety and efficacy data for an NDA application with an indication of temporary relief of the signs and symptoms of dry eye disease. Based on the summary clinical data provided in the meeting package, it did not appear that the applicant had adequate and well-controlled trials to support the approval of an NDA. While STRIDE 1 (Study KPI-121-C-006) appeared to meet its coprimary sign and symptom endpoints, the results were not replicated in STRIDE 2 (Study KPI121-C-007). Study KPI-121-C-002, the Phase 2 trial, also failed to meet its co-primary sign and symptom endpoints.

Kala submitted a new drug application for KPI-121 0.25% on October 15, 2018. On August 7, 2019, Kala received a complete response letter (CRL) from the Agency, in which the need for an additional adequate and well controlled clinical trial was noted. The results from an additional Phase 3 trial (STRIDE 3; KPI-121-C-011) are included in this Class 2 resubmission for the application.

3.3. Foreign Regulatory Actions and Marketing History

At the time of this submission, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% has not been marketed in any region globally.

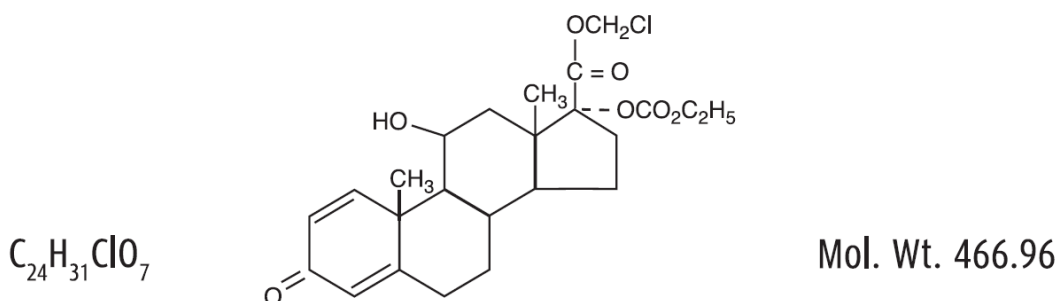
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) completed a review dated 6/14/2019. The clinical sites of Drs. Whitsett, Rauchman, and Nichols were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007) appear to have been conducted adequately. The final compliance classifications of the inspections of Drs. Whitsett, Rauchman, and Nichols were No Action Indicated (NAI). The Division did not request additional OSI inspections for study KPI-121-C-011.

4.2. Product Quality

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is a sterile aqueous suspension of loteprednol etabonate (LE) for topical ophthalmic use. Each milliliter contains 2.5 mg LE as the active ingredient. Loteprednol etabonate is represented by the following structural formula:



The quantitative composition and function of each component in EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is listed in the following table.

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Table 2 - Composition of EYSUVIS 0.25%

Ingredient	Quality Standard	Function	Amount (mg) in each mL of EYSUVIS 0.25%	Concentration (%w/v) in EYSUVIS 0.25%
Loteprednol etabonate	(b) (4)	Active Pharmaceutical Ingredient	2.5	0.25
Glycerin	USP-NF	(b) (4)		
Sodium citrate, dihydrate	USP-NF			
Sodium chloride	USP-NF			
Poloxamer 407	USP-NF			
Edetate disodium, dihydrate	USP-NF			
Citric acid (b) (4)	USP-NF			
Benzalkonium chloride	USP-NF	Preservative	0.1	0.01
Water for injection	USP-NF	(b) (4)		
(b) (4)				
(b) (4)				
USP-NF: United States Pharmacopeia - National Formulary				
(b) (4)				

Source: Module 2.3.P

Table 3 - Quality control specifications for release of EYSUVIS 0.25% commercial fill bottles

Attribute and Test	Method Number	Acceptance Criteria
Appearance	(b) (4) Visual Observation	White dropper bottle (b) (4)
pH	(b) (4)	
Osmolality		
Benzalkonium Chloride Assay		
Particle Size Distribution		
Minimum Fill Volume	USP<755>	(b) (4)
Identity Loteprednol Etabonate (LE)	(b) (4)	
Assay Loteprednol Etabonate		

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Attribute and Test	Method Number	Acceptance Criteria
Loteprednol Etabonate related impurities ¹ A. Loteprednol Etabonate related substances and impurities B. Total of all related impurities	(b) (4)	
EDTA Assay		
Sterility	USP<71>	Meets USP test requirements

NMT = Not More Than; (b) (4), EDTA = edetate disodium, dihydrate
 (b) (4)

Source: Module 2.3.P

The container closure system for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% consists of a white low-density polyethylene (LDPE) plastic bottle with nominal capacity of 10 mL; a controlled-drop, linear LDPE (LLDPE) tip; and a pink high-density polyethylene (HDPE) 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.

NDA 210933 was recommended for approval from Product Quality perspective on Feb 22, 2019. No product quality update was submitted in the resubmission.

All the manufacturing facilities remain acceptable. An overall acceptable recommendation for all the facilities was issued on Aug 24, 2020. NDA 210933 has been recommended for approval from Product Quality perspective.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

Loteprednol etabonate (LE) is a corticosteroid ester initially approved in 1998 (Bausch & Lomb's NDA 20-583 for LOTEMAX). From a nonclinical perspective, the NDA relies on Kala's own studies, and FDA's finding of safety for the approved listed drug LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 20-583. The nonclinical Pharmacology/Toxicology (P/T) review identified no new safety concerns for EYSUVIS.

4.5. Clinical Pharmacology

Study KPI-121-C-009 characterized the PK exposure of LE in 20 healthy adult subjects. Plasma concentrations of LE, and the inactive metabolites, PJ-90 and PJ-91, were analyzed using a validated LC/MS/MS method. The analytical ranges of the assay were validated from 1.00 to 1,000 ng/mL for LE and PJ-91 and the lower limit of assay quantitation (LLOQ) was 1.00 ng/mL. The analytical ranges of the assay were validated from 5.00 to 5,000 ng/mL for PJ-90 and the LLOQ was 5.00 ng/mL.

All plasma concentrations of LE, PJ-90, and PJ-91 at every time point pre-and post-instillation of 2 drops of EYSUVIS 0.25% in each eye QID for 15 days were BLQ (Below the Limit of Quantitation). Thus, the Applicant was unable to characterize the PK parameters for LE, PJ- 90, and PJ-91.

4.6. Devices and Companion Diagnostic Issues

There are no device or companion diagnostic issues for this application.

4.7. Consumer Study Reviews

There are no consumer study reviews for this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 4 - Table of Clinical Studies

Protocol Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects ^a	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Trial Status; Type of Report
<i>Module 5.3.3.1 – Healthy Subject PK and Initial Tolerability Study Reports</i>							
KPI-121-C-009	Systemic PK of LE and its major metabolites, PJ-90 and PJ-91	Phase 1, single center, open-label, PK study of KPI-121, no control group	KPI-121 0.25% QID 2 drops OU	20 total	Healthy adults	15 days	Completed Full
<i>Module 5.3.5.1 – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication</i>							
KPI-121-C-002	Efficacy and safety of KPI-121 compared to vehicle	Phase 2, multi-center, randomized, double-masked, parallel-group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	150 total: 73 KPI-121 0.25% 77 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	28 days of treatment preceded by a 14-day vehicle run-in period	Completed Full
KPI-121-C-006 (STRIDE 1)	Efficacy and safety of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel-group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	915 total: 459 KPI-121 0.25% 456 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	14 days of treatment preceded by a 14-day vehicle run-in period	Completed Full
KPI-121-C-007 (STRIDE 2)	Efficacy and safety of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel-group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	905 total: 452 KPI-121 0.25% 453 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	Efficacy and safety of KPI-121 compared to vehicle	Completed Full
KPI-121-C-011 (STRIDE 3)	Efficacy and safety of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel-group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	901 total 447 KPI-121 0.25% 454 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	Efficacy and safety of KPI-121 compared to vehicle	Completed Full
<i>Module 5.3.5.4 – Other Study Reports</i>							

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Protocol Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects ^a	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Trial Status; Type of Report
KPI-121-C-001	Efficacy and safety of 2 concentrations of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel-group study of 2 concentrations and dosing regimens of KPI-121 vs. vehicle	KPI-121 0.25% QID KPI-121 1% BID Vehicle A QID Vehicle B BID 1 to 2 drops in the study eye	380 total: 125 KPI 121 1% 129 KPI-121 0.25% 126 Vehicle ^b	Male and female subjects age ≥18 years who had undergone routine cataract surgery	14 days	Completed Full
KPI-121-C-003	Efficacy and safety of KPI-121 compared to vehicle	Phase 2, multi-center, randomized, double-masked, parallel-group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	205 total: 104 KPI-121 0.25% 101 Vehicle	Male and female subjects age ≥18 years with signs and symptoms of inflammatory MGD	28 days of treatment preceded by a 14-day vehicle run-in period	Completed Abbreviated
KPI-121-C-004	Exploratory safety and efficacy of 2 concentrations of KPI-121	Exploratory, multi-center, randomized, single-masked, parallel-group study of 2 concentrations of KPI-121	KPI-121 1% QID KPI-121 0.25% QID 1 to 2 drops in the study eye	15 total: 9 KPI-121 0.25% 6 KPI-121 1%	Male and female subjects age ≥ 18 years with documented presence of intraretinal or subretinal fluid secondary to RVO or DME	28 days	Completed Synoptic

BID = twice daily; DED = dry eye disease; DME = diabetic macular edema; KPI = Kala Pharmaceuticals, Incorporated; LE = loteprednol etabonate; MGD = meibomian gland disease; OU = both eyes; PK = pharmacokinetic; QID = four times daily; RVO = retinal vein occlusion

^a Number of subjects is presented for the safety population, which is defined as all randomized subjects receiving study treatment and having at least one postbaseline safety assessment.

^b Number of subjects in the Vehicle group in Study KPI-121-C-001 was the total for Vehicle groups A and B, which were pooled for all analyses.

5.2. Review Strategy

The primary evidence of efficacy reported within this new drug application to support EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% for the temporary relief of the signs and symptoms of dry eye disease is based on data from 4 multicenter, double-masked, randomized, vehicle-controlled dry eye trials (Trials KPI-121-C-002, KPI-121-C-006, KPI-121-C-007, KPI-121-011). All 4 dry eye trials in the original application included 2 treatment groups: KPI-121 0.25% QID and vehicle QID. Trial KPI-121-C-002 included a 28-day treatment period, and Trials KPI-121-C-006, KPI-121-C-007 and KPI-C-011 included 14-day treatment periods. In all 4 trials in the original application, a run-in period preceded the treatment period wherein all subjects applied KPI-121 vehicle QID for 2 weeks.

6. Review of Relevant Individual Trials Used to Support Efficacy

For a detailed discussion of Trials KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007, see the original Medical Officer's review in DARRTS dated July 29, 2019.

6.1. Trial KPI-121-C-011

A Phase 3, Double-masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease (STRIDE 3)

6.1.1. Study Design

Overview and Objective

The primary objective of the study was to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects who had a documented clinical diagnosis of dry eye disease.

Trial Design

This was a Phase 3, multicenter, double-masked, randomized, vehicle-controlled, parallel-group study designed to evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension in treating the signs and symptoms of dry eye disease. This study included up to 4 clinic visits, including 2 weeks of single-masked vehicle run-in followed by up to 2 weeks of study treatment dosing (KPI-121 0.25% ophthalmic suspension or vehicle).

2842 subjects were evaluated for eligibility at Screening in order to randomize approximately 900 subjects. Subjects meeting eligibility criteria at Screening (Visit 1) entered a 14 ± 1 day run-

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in period of four times daily (QID) dosing with single-masked vehicle in both eyes. On Day 1 (Visit 2), subjects who continued to meet eligibility criteria were randomized in an approximate 1:1 ratio to either KPI-121 0.25% ophthalmic suspension or vehicle dosed QID in both eyes. Subjects returned to the clinic at Day 8 (± 1 day; Visit 3) to review diary data, evaluate eye dryness, and report concomitant medication use and adverse events (AEs). Subjects returned to the clinic at Day 15 (± 1 day; Visit 4) for a complete study evaluation, discontinuation of dosing, and study exit. Bottles of study treatment were dispensed at designated visits based on the subject's randomization.

Randomization was stratified at baseline based on study qualification criteria entered into the interactive web recognition system (IWRS), as follows:

- Ocular discomfort severity (ODS) scores of low (> 40 mm to < 68 mm) or high (≥ 68 mm to 100 mm) based on the subject's rating of ODS on the day prior to Day 1; and
- Investigator-rated bulbar conjunctival hyperemia scores of low (2) or high (≥ 3) in the eye with the higher score at Day 1.

Table 5 - Summary of Procedures KPI-121-C-011

Procedures	Stage 1	Stage 2		
	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	Randomization	Diary Collection Visit	End of Study Visit
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (+2 days)
Informed Consent, HIPAA and Significant Medical History	X			
Subject-rated assessment of ocular discomfort (in office)	X			
Subject-rated assessment of ocular discomfort (subject diary)		X ^c	X ^c	X ^c
Subject-rated assessment of eye dryness (in office)		X	X	X
Concomitant medication query	X	X	X	X
Urine Pregnancy Test ^a	X			X
Inclusion/Exclusion	X	X		
AE Assessment	X	X	X	X
Investigator-rated assessment of bulbar conjunctival hyperemia	X	X		X
Bulbar conjunctival hyperemia photography		X		X
BCVA	X	X		X
Slit lamp biomicroscopy	X	X		X
Corneal fluorescein staining	X	X		X
Unanesthetized Schirmer Test Assessment	X			
IOP measurement	X	X		X
Dilated ophthalmoscopy	X			X
Investigational product administration in-clinic	X ^b	X		
Dispense investigational product	X ^b	X		
Dispense subject diary	X ^b	X	X	
Collect investigational product		X ^b		X
Collect subject diary		X	X	X

AE = adverse event; BCVA = best corrected visual acuity; HIPAA = Health Insurance Portability and Accountability Act; IOP = intraocular pressure

^a Women of childbearing potential only

^b Stage 1 Product

^c Collected through use of subject diary

Study Endpoints KPI-121-C-011

The trial had 2 primary efficacy endpoints:

- Change in ODS scores in the ITT population, calculated as the mean of the scores recorded in the subject's diary for the 3 days prior to Day 15 minus the mean for the 3 days prior to Day 1.

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- Change in ODS scores in the ITT subgroup with more severe baseline ocular discomfort (defined as subjects with ODS score ≥ 68 mm 1 day prior to Day 1), calculated as the mean of the scores recorded in the subject's diary for the 3 days prior to Day 15 minus the mean for the 3 days prior to Day 1.

Inclusion/Exclusion Criteria KPI-121-C-011

Inclusion/Exclusion Criteria were Identical to criteria for STRIDE 1 and STRIDE 2.

Investigational Products KPI-121-C-011

Investigational Products were Identical to those used in STRIDE 1 and STRIDE 2.

Statistical Analysis Plan KPI-121-C-011

The ITT population was defined as all randomized subjects who received at least 1 dose of randomized study treatment. The subjects were analyzed as randomized, i.e., according to the planned treatment.

The PP population was defined as subjects who completed the randomized study treatment period from Visit 2 through Visit 4, achieved reasonable compliance with the study protocol, and had no major protocol violations. Subjects were analyzed as treated.

The safety population was defined as all randomized subjects who received at least 1 dose of the randomized study treatment (starting at the Day 1 visit) and from whom at least 1 safety assessment was obtained after randomization. The safety population was analyzed for all safety assessments. Subjects were analyzed as treated.

All efficacy comparisons were performed between the KPI-121 0.25% ophthalmic suspension group and the vehicle group. All efficacy endpoints were summarized for the ITT population, or a subgroup of the ITT population as defined for the endpoint. Primary efficacy endpoints were also summarized using the PP population.

The primary efficacy endpoint comparisons were performed between the KPI-121 0.25% ophthalmic suspension group and the vehicle group using a Hochberg procedure, wherein a step-up procedure was used, starting with the largest p-value compared to the largest endpoint-specific critical value (α). The overall alpha level was set to 0.05.

In addition, several secondary endpoints were designated per the statistical analysis plan. Post hoc and other efficacy analyses were also conducted.

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Investigators KPI-121-C-011

Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
138	Jack Abrams, MD	Tapan R. Shah, MD Lindsey Szeto, CCRC Katie Kowal, CCRC	Abrams Eye Institute 6450 Medical Center Street, Suite 100 Las Vegas, NV 89148	13/11/0
137	Marc Abrams, MD	None	Abrams Eye Center 2322 E. 22nd Street Suite 102 Cleveland, OH 44115	32/7/0
140	Louis Alpern, MD	Lawrence C. R. Tafoya, MD Teresa Cintron, COA	The Cataract & Glaucoma Center 4171 North Mesa Street Building D, Suite 100 El Paso, TX 79902	52/33/0
163	Carol Aune, OD	Tonica V. Johnson, MD Jennifer Newsome Erik Aune	Oculus Research, Inc. at Eyecare Center 4170 Fayetteville Road Raleigh, NC, 27603	64/14/0
269	Robert Benza, MD	Radhika L. Kumar, MD Candace D. Hayes	Apex Eye 10615 Montgomery Road, Suite 202 Cincinnati, OH 45242	7/5/0
126	Gregg Jonathan Berdy, MD, FACS	Ranjan P. Malhotra, MD, FACS Robert C. Brusatti, OD Andrew Royer, OD Deborah Gravemann, RN, CCRP Dawn Wiemers, BS, MBA	Ophthalmology Associates 12990 Manchester Road Suite 200 St. Louis, MO 63131	29/10/0
142	Mark T. Bergmann, MD	Daniel John Hammer, MD Erik C. Kuntzsch, OD Merissa Strack Toni Cole Aly Collopy	Marl T. Bergmann, MD 6507 Harrison Avenue Suite E Cincinnati, OH 45247	32/1/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
143	James Boyce, MD	Norman Liu, MD Ryan Taban, MD Gladys Sager, CCRC	Orange County Ophthalmology Medical Group 12665 Garden Grove Boulevard, Suite 401 Garden Grove, CA 92843	82/52/0
279	David Brown, III, MD	Claudio A. Ferreira, MD Juan Fernandez de Castro, MD Eric Eiselman OD	Eye Centers of Florida 4101 Evans Avenue Fort Myers, FL 33901	7/0/0
184	Leonard Robert Cacioppo, MD	James Richard Jachimowicz, MD	Hernando Eye Institute 14543 Cortez Boulevard, Brooksville, FL, 34613	22/7/1
277	Lisa Marie Cibik, MD, FACS	John P. Naim, MD Sean Pieramici, MD Brian A. Moore, OD Ryan McBee, OD Lesley M. Holot Amber Shirer Carly Ackman	Associates in Ophthalmology 9970 Mountain View Drive, Suite 200 West Mifflin, PA 15122	1/0/0
273	Emma L. Clay, MD	Carl T. Hartman, MD Trinh T. Nhu, MD Theodore A. Pasquali, MD Kevin Kwok, OD	SoCal Eye 3300 E. South Street Suites 100, 105 Long Beach, CA 90805	83/37/0
268	Douglas G. Day, MD	Suzanne M. Hewitt, MD	Coastal Research Associates, LLC 11205 Alpharetta Highway Suite J3 Roswell, GA 30076	13/6/0
281	Peter DeBry, MD	Andy Mu, OD Erin Fox Kaylee Rosenbusch Selma Luedtke Pinoi Bouddhabandith	NV Eye Surgery 2390 W. Horizon Ridge Parkway, Suite 100 Henderson, NV 89052	25/1/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
250	Robert Deitch, MD	Stephen Johnson, MD Blair Boehmer, MD Mary Adams Angela Roberts	Midwest Cornea Associates, LLC 10300 N. Illinois Street Suite 1020 Indianapolis, IN 46290	12/5/0
146	Michael Depenbusch, MD	Frank Caserta, MD Erin Fox Kaylee Rosenbusch Guadalupe Robles Crystal Brown Heather Yoshimura David Tatelbaum Lindsey Arcuri	Arizona Eye Center 1500 W. Ray Road, Chandler, AZ, 85224	80/17/0
283	Johnathon Eric Downing, MD	Michelle A. Sato, MD Alex C. Liu, MD James Masunaga Ilanie Shiell Anthony Vazquez Natalie Ly	East West Eye Institute, Inc. 420 East Third Street Suite 603 Los Angeles, CA 90013	31/13/0
136	Harvey DuBiner, MD	Ronald Weber, MD Daniel I. Strait, OD Jennifer Kim, MD Brenton D. Smith, OD Helen DuBiner, PharmD, CCRC Jean Jouffroy Trung Bui Carey Phlong, OD Heather Ambrosia, OD Ethan Seville, CCRC Tiffany Sims Ratana Kong Peter Chen, OD, PhD Thuy Ngo Yvonne Nguyen	Clayton Eye Clinical Research, LLC 1000 Corporate Center Drive Suites 100, 120 Morrow, GA, 30260	29/13/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
147	Sherif M. El- Harazi, MD	Lilit Minasyan, MD Jamie Zepeda Norman Maldonado Aleen Haroutunian Omar Karram Lugene El-Harazi	Global Research Management 1510 South Central Avenue, Suite 300 Glendale, CA 91204	143/38/2
127	David G. Evans, OD	Eugene B. McLaurin, MD, FACS Don W. Gayso, OD Brandon Rushing, OD Daniel J. Ashe Kim Smith Kaitlyn McCalmon Ariel McNatt Roxanne Barnett	Total Eye Care, PA 6060 Primacy Parkway Suite 200 Memphis, TN 38119	106/50/0
176	Richard Evans, MD	Jason Burns, MD Michael Orozco, OD Brian Mathews, SC	Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240	20/0/0
282	Anna Fakadej, MD	John D. Miller, OD Lisa Fulghum Brittany Aichele I McLaughlin Brandy Wallace Nicholas Leonard	Carolina Eye Associates 2170 Midland Road Southern Pines, NC 28387	23/11/0
217	Asra Firozvi, MD	Jackquelyn Bell Tameka Cooper	Firozvi Research, LLC 4102bN. Roxboro Road Durham, NC 27704	31/19/1
105	Raymond Fong, MD	Douglas B. Friedrich, MD David Yip, OD Timothy Ip, OD Albert Yuen Jenny Kam Pow Yee Kok	Raymond Fong, MDPC 109 Lafayette Street, 4th Floor New York, NY 10013	16/7/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
102	James Zachary Forsey, MD	Michael Tepedino, MD Michael Evans, MD Teresa Grimberg Yoon J. Choe	Wake Forest Health Network Ophthalmology – Oak Hollow 1400 East Hartley Drive High Point, NC 27262	15/1/0
218	S. Lance Forstot, MD	Karen Repine, MD Robert Fish, MD Bradley Gustave, MD Michael Wildes, MD Breanna Nickels, CCRC Melanie Fortin Andy Humes Wendy Bigger	Corneal Consultants of Colorado 8381 Southpark Lane Littleton, CO 80209	21/2/0
106	Joseph Gira, MD	Erin Sullivan, OD Michelle Derheimer, OD Stephanie Williams Amy Young	Ophthalmology Associates, Ltd 12990 Manchester Road Saint Louis, MO 63131	28/17/0
107	Damien Goldberg, MD	Barry Wolstan, MD Jennifer Picone- Jones Kayla Wiley	Wolstan & Goldberg Eye Associates 23600 Telo Avenue, Suite 100 Torrance, CA 90505	44/15/2
230	John Goosey, MD	Jeffrey Arnoult, MD Susan Wittenberg, MD	Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	0/0/0
219	Jack Greiner, OD, PhD, DO, MS	Paula J. Oliver	Clinical Eye Research of Boston 955 Main Street, #307 Winchester, MA 01890	23/9/0
148	Robert H. Gross, MD	Jung T. Dao, MD Julie Komer Katherine Zakrzewski	Cornea & Cataract Consultants of Arizona 3815 E. Bell Road #2500 Phoenix, AZ 85032	33/15/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
149	Preeya Gupta, MD	Victor Lucas Perez Quinones, MD Alice Ventura Loretta Foraker Elmer Balajonda Roy McDonald Malina Sexton	Duke University Duke Eye Center 2351 Erwin Road Durham, NC 27710	2/0/0
168	Mohammed Ali Haider, DO	Aron McNulty, OD Ashley Griffith, BS Sheeraz Naqvi, BS Jennifer Yarber	Senior Health Services 2932 Breckenridge Lane Suite 5 Louisville, KY 40220	87/28/1
266	Jennifer Harthan, OD	Osvaldo Lopez, MD Stephanie Fromstein, OD Michelle Man, OD	Illinois College of Optometry 3241 S. Michigan Avenue Chicago, IL 60616	29/5/0
108	Paul James Hartman, MD	Alan H. Gruber, MD Mindy VanVoorhis, CCRC Melissa Hart, CCRC Rachel Rivera, COA Michelle Hurley, COA Michelle Dunn, COA	Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618	26/1/0
278	Sebastian Heersink, MD	Marnix Heersink, MD Harsha Sen, MD Jordan Johnson, OD Emily Ivey Jessica Shirley Scarlett Duffie Ariel Tillman	Trinity Research Group 2800 Ross Clarke Circle Dothan, AL 36301	4/3/0
185	Milton M. Hom, OD FAAO	Kavita Surti, MD Angela Zermeno Nathalie Bernabe Deborah Beltran	Milton M. Hom, OD, FAAO 822 E. Alosta Avenue Suite A Azusa, CA, 91702	75/32/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
264	Edward K. Isbey, III, MD	William Haynes, MD Brian Edward Smith, MD Jeffery Schultz, OD R. Benjamin Meade, OD, MS Stephanie Brien, OD Lea Renee Raymer Rebecca Michelle Keener McCayla Hall Ashley Donecho Denise Ammons	Asheville Eye Associates, PLLC 8 Medical Park Drive Asheville, NC 28803	5/2/1
151	Mitchell A. Jackson, MD	Anna Edmiston, MD Gabriela Trabal, MD	Jackson Eye SC 300 N. Milwaukee Avenue Suite L Lake Villa, IL 60046	50/11/0
274	Paul Karpecki, OD	Johannes Evans, MD Bryant Evans OD	Kentucky Eye Institute 601 Perimeter Drive Lexington, KY 40517	0/0/0
259	Lucy Kehinde, OD	Eric Ritchey, OD, PhD Nick Holderman, OD, MD	University of Houston - College of Optometry 4901 Calhoun Road Houston, TX 77204	30/7/0
128	Kathleen A. Kelley, OD	Francis Price, Jr, MD Faye Peters, OD Clorissa Quillin Marianne Price	Price Vision Group 9002 North Meridian Street Suite #100 Indianapolis, IN 46260 Cornea Research Foundation of America 9002 North Meridian Street Suite 212 Indianapolis, IN 46260	11/4/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
131	Michael S. Korenfeld, MD	Matthew R. Lazarus Michelle M. Mueller Brooke M. Wideman	Comprehensive Eye Care, Ltd 901 East 3rd Street Washington, MO 63090	35/7/0
186	John F. Kozlovsky, MD	Richard L. Delay, OD Jeannine E. Camacho, OD	Kozlovsky Delay & Winter Eye Consultants, LLC 2929 Mossrock, Suite 104 San Antonio, TX 78230	26/8/0
263	Eva Liang, MD	Michael Pernula, MD Jeffery Hart, MD Jeylan EL Mansoury, MD Adam Schwartz, OD Tina Licina, OD George Bouras, OD	Center for Sight 330 S. Rampart Boulavard Suite 360 Las Vegas, NV 89145	4/0/0
247	Thomas David LoBue, MD	Ryan G. Miller, OD Erin Schaefer, COA	LoBue Laser and Eye Medical Center 40700 California Oaks Road, Suite 106 Murrieta, CA 92562	31/1/0
187	Parag Majmudar, MD	Maria Rosselson, MD Tiffany Andrzejewski, OD Brian Doyle, OD Charles Faron, OD James Nykaza Cristina Bosler	Chicago Cornea Consultants, Ltd 1585 N. Barrington Road Suite 502 Hoffman Estates, IL 60169	22/7/0
111	Joseph Martel, MD	James B. Martel, MD Liliya Golas, MD Nataliya Karpach Sabrina Vangkhue Carrie Xiong Stephanie Diaz	Martel Eye Medical Group and Surgical Center 11216 Trinity River Dr. Rancho Cordova, CA 95670	100/38/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
171	Edward John Meier, MD	Leon A. Reid, III, MD Shannon Back Tina Winward Samantha Huff Christina Hughes	Apex Eye 6150 Radio Way Mason, OH 45040	33/5/0
195	John Meyer, MD	Guruprasad R. Pattar, MD, PhD Brennan P. Greene, MD Mandy Kessinger Kellye Johnson Angela Warfield Spencer Holley William Blair	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	39/8/0
270	Joseph Meyer, MD	Samantha Boldt, COA Thomas Dykes Tamatha Hartley	Round Rock Eye Consultants/Revolution Research 1880 Round Rock Avenue Suite 100 Round Rock, TX 78681	27/7/0
132	Michelle Mijares, OD	Jason Todd Flicker, MD Howard Adam Lane, MD Cara Fidnarick Mary Modica Janet Bulit Denise Grosso	South Shore Eye Care, LLP 2185 Wantagh Avenue Wantagh, NY 11793	27/14/0
280	Steven Mortenson, MD	Scott Markham, DO James Arthur, MD Byron Tabbut, MD Rachel Wells, OD Brett Christensen, OD Erin Fox Kaylee Rosenbusch Heather Yoshimura Sheri Compson Crystal Brown Ashley Buschman	M & M Eye Institute 3192 Willow Creek Road Prescott, AZ 86301	34/5/1

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
133	Kelly Kinney Nichols, OD, MPH, PhD, FAAO	Robert P. Kimberly, MD Jillian F. Ziemanski, OD, MS John Laurent, OD, PhD, FAAO Emily Deng	University of Alabama at Birmingham School of Optometry Henry Peters Building 1716 University Blvd Suite 403 Birmingham, AL 35294	66/7/0
188	Yen Dang Nieman, MD	Thomas Richard Walters, MD Robert Edward Marquis, MD Blythe Elizabeth Monheit, MD Sarah Benedict Jamie Johnson Tracey Knox Elaine Marcin Jess Lieblich Jennifer Cooper	Keystone Research 5717 Balcones Drive Austin, TX 78731	32/7/0
155	James Peace, MD	Carmelina Marin Xyryl De Leon Evelyn Alvarez	United Medical Research Institute 431-433 N. Prairie Avenue Inglewood, CA 90301	35/17/1
189	Bernard R. Perez, MD, FACS	Don J. Perez- Ortiz, MD, FACS Gelissa Mann, CRC Natalia Gallego, CRC Michelle Whidden, CCRC	International Research Center 4506 Wishart Place Tampa, FL 33603	33/0/0
258	Edward R. Rashid, MD	William J. Flynn, MD Charles D. Reilly, MD Gregory Brunin, MD Catherine Hazen Griselda Rodriguez Michelle Jackson	R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	49/4/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
130	Steven Rauchman, MD	Robert Smyth-Medina, MD Joanne Perry Rocio Rodriguez Cecilia Casas Marie Contreras Christie Delgadillo Sandra Mejia	North Valley Eye Medical Group 11550 Indian Hills Road Suite 341 Mission Hills, CA 91345	39/18/0
156	Harvey J. Reiser, MD	Richard Evan Roth, DO Carrie Allgeier Cardillo, OD Kristen Lauren Epting, OD Patti J. Myers Patty Yuhas Alexander Zubko Gary Stavish	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704	10/4/0
174	Vincent Restivo, Jr., MD	Nathan Osterman, OD Sheila Nardelli, MMSc, COA Jerome Gomez Bev Dvorak, MBA	Hill Country Eye Center 11901 West Parmer Lane Suite 400 Cedar Park, TX 78613	30/8/0
175	Kyle Rhodes, MD	Tommy Dang, Jr., MD Samantha Boldt, COA Thomas Dykes Tamatha Hartley	Lake Travis Eye and Laser Center 3503 Wild Cherry Drive Building 3 Lakeway, TX 78738	47/17/0
222	Trent D. Richards, MD	Jean Bennett, BS, MPH Rachel Gardner BS, CRC Melanie Gibb, CCRC Kali Sargent, CRC Stephanie Smith, CRC	Tanner Clinic 1756 W. Antelope Drive Layton, UT 84041	20/4/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
265	Jerry Robben, OD	Frank W. Bowden, III, MD, FACS Sarah Darbandi, MD Kevin Cronin, MD Natasha Kryanowski, OD Philip Griffith, OD Jessica Montgomery, COA, CCRC Holly Stiffler, COT Armani Blue	Bowden Eye & Associates 7205 Bonneval Road Jacksonville, FL 32256	39/5/0
190	Jay Rubin, MD	David Shulman, MD Sharon K. Sra, MD Ervin Mendlovitz, OD Lori Colon Marcie Smith Yasmin Pena	Eye Clinics of South Texas 999 E. Basse Road Suite 128-B San Antonio, TX 78209	20/5/0
262	Bruce Segal, MD	Talya H. Kupin, MD	Bruce Segal, MD 5258 Linton Boulevard Suite 302 Delray Beach, FL 33484	46/19/0
271	Michael Sheety, MD	Valerie Pilon, OD Isabel Rubio, CRC Pooja Patel, CRC	Sierra Clinical Trials Research Organization 2010 E. First Street Santa Ana, CA 92705	36/18/0
119	John D. Sheppard, MD, MMSc	Walter O. Whitley, OD Christopher Kruthoff, OD Brienne Spencer, CCRC Lisa Dyer, CCRC Christin Thompson	Virginia Eye Consultants 241 Corporate Boulevard Suite 210 Norfolk, VA 23502	6/1/0
157	Philip Lee Shettle, DO	None	Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	34/18/0
200	David Irving Silbert, MD, FAAP	Heather F. Modjesky, COE	Conestoga Eye 2104 Spring Valley Road Lancaster, PA 17601	14/1/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
158	Steven M. Silverstein, MD	Timothy M. Stout, MD Jeff L. Lookhart, OD Alyssa Stevens Shala Holzchuh Sonia Rowland Cindy Bentley	Silverstein Eye Centers 4240 Blue Ridge Boulevard Suite 1000 Kansas City, MO 64133	30/1/0
272	Robert C. Sorenson, MD, PhD	Barratt L. Phillips, MD Sara Khandan, MD Norlisha Borntrager Jazmin Briones	Inland Eye Specialist 3953 W. Stetson Avenue Hemet, CA 92545	22/1/0
240	Terrence Spencer, MD	Stephen Khachikian, MD Bailey DeBaere, SC Brianna Coyne, SC	Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701	31/5/0
191	Nancy Stephens, OD	William Lipsky, MD, Teresa M. Solis, CCRP Barbara N. Lund	Advanced Laser Vision & Surgical Institute 11550 Fuqua Street Suites 215 & 250 Houston, TX, 77034	53/30/0
275	Matthew Swanic, MD	Gregory Hsu, DO Lindsey Szeto Katie Kowal	Las Vegas Eye Institute 9555 S. Eastern Avenue Suite 260 Las Vegas, NV 89123 AdvanceMed Clinical Research 8565 S. Eastern Avenue Suite 102 Las Vegas, NV 89123	19/6/0
121	Joseph Tauber, MD	Crystal Remington, OD, FAAO	Tauber Eye Center 4400 Broadway, Suite 202 Kansas City, MO 64111	14/5/0
123	Navin Tekwani, MD	Hiralal Tekwani, MD Jessica Jones OD Lisa Dinsmore Alexandria Prunty Lisa Schepp	Tekwani Vision Center 9911 Kennerly Road Suite A St. Louis, MO 63128	21/12/0

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Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
213	Michael Khanh Le Tran, MD, FACS	Uyen Tran Rachelle Trinh Thanh N. Mai	Michael K Tran, M.D., Inc 15355 Brookhurst Street, Suite 104 Westminster, CA, 92683	22/7/0
182	Da-Thuy Van, DO	Bernard A. Milstein, MD Chance Caddell Angie Carter	The Eye Clinic of Texas, an affiliate of Houston Eye Associates 1100 Gulf Freeway Suite 114 League City, TX 77573	24/3/0
276	Gerald Walman, MD	Erin Fox Kaylee Rosenbusch Lindsey Arcuri Steven Shively Heather Yoshimura Crystal Brown Sheri Compson Brianna Hernandez	Walman Eye Center 10615 West Thunderbird Boulevard D180 Sun City, AZ 85351	34/2/0
124	Jeffrey Whitsett, MD	Jesse McKey, MD David Fu, OD	Whitsett Vision Group 1237 Campbell Road Houston, TX 77055	10/8/0
125	Steven M. Wilson, OD	Howard S. Lazarus, MD Kaylea Janel Lipps, OD Liana Davis, LPN, COA Debra Paige Bunch, COA	John-Kenyon American Eye Institute 519 State Street New Albany, IN 47150	14/7/0

Clinical Review

William M. Boyd, M.D.

NDA 210933 Class 2 resubmission

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Site No.	Investigator Name	Sub- Investigator(s) Name	Address	Enrolled/Randomized/ Early Study Withdrawal
215	David L. Wirta, MD	David Salvay, MD Linda Wirta Yvette Abbascia Heather Tyner Haley Noel Jenny Ryan Kimberly Abbascia Madison Haly William Kiely Mai Giang Chelsea Vesely Melinda Fischer Tina Johns	Eye Research Foundation 520 Superior Avenue Suite 235 Newport Beach, CA, 92663	90/27/0
224	Daniel V. Zimmer, MD, FACS	William C. Christie, MD Natasha Hindman, OD George J. Grisnik, OD	Scott & Christie and Associates, PC 105 Brandt Drive Suites 201, 202 Cranberry Township, PA 16066	88/25/0

6.1.2. Study Results KPI-121-C-011

Compliance with Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Financial Disclosure

See Appendix 13.2 of this review.

Clinical Review

William M. Boyd, M.D.

NDA 210933 Class 2 resubmission

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Patient Disposition KPI-121-C-011

	KPI-121 0.25% (N=447)	Vehicle (N=454)	Total (N=901)
Completed Study	437 (97.8%)	453 (99.8%)	890 (98.8%)
Subjects Withdrawn Early from the Study	10 (2.2%)	1 (0.2%)	11 (1.2%)
Reason for Study Exit			
Adverse event	3 (0.7%)	0	3 (0.3%)
Withdrawal by subject	3 (0.7%)	0	3 (0.3%)
Lost to follow-up	1 (0.2%)	1 (0.2%)	2 (0.2%)
Other	3 (0.7%)	0	3 (0.3%)

ITT = intent-to-treat

Source: Table 14.1.2.1

A total of 2842 subjects were screened for the study; of these, 1941 were screening or randomization failures (i.e., subjects who failed to meet eligibility criteria at Visit 1 or at Visit 2) and 901 were screen successes and were randomized into the trial. Included in these 901 randomized subjects were 3 individuals who previously completed one of the other phase 3 trials, KPI-121-C-007, and then enrolled in this trial (Listing 16.2.1.5; Subjects (b) (6); their data were included in all applicable analyses, but they were exited from the study at Visit 2 (see below).

Of the 901 subjects in the ITT population, 447 were randomized to treatment with KPI-121 0.25% and 454 were randomized to treatment with vehicle. Of the 901, 890 subjects (99%) completed the study and 11 subjects (1%) discontinued (10 in the KPI-121 group and 1 in the vehicle group; Table 7). In the KPI-121 0.25% group, 3 subjects exited due to AE, 3 subjects withdrew consent, 3 subjects discontinued due to “other” reasons (all of whom were randomized into the study in error at Visit 2, following incomplete compliance or following prior participation in Trial KPI-121-C-007), and 1 subject was lost to follow-up. In the vehicle group, 1 subject was lost to follow-up.

The first subject was randomized on 23 Jul 2018 and the last subject exited the study on 05 Feb 2020.

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Protocol; Violations/Deviations KPI-121-C-011

Deviation Type	KPI-121 0.25% (N=447)	Vehicle (N=454)
Study Product Deviation	202 (76.2%)	196 (75.4%)
Other	60 (22.6%)	54 (20.8%)
Study Visit Schedule Deviations	47 (17.7%)	68 (26.2%)
Missed Procedures	31 (11.7%)	23 (8.8%)
Inclusion & Exclusion Criteria	21 (7.9%)	21 (8.1%)
Concomitant Medication Deviation During Stage 2	4 (1.5%)	2 (0.8%)
Qualification for Randomization	1 (0.4%)	3 (1.2%)

ITT = intent-to-treat

Source: [Table 14.1.7](#)

The “other” deviations were commonly related to the timing of study procedures (e.g., not enough time between Schirmer and fluorescein staining) or incorrect site staff involved in a procedure (e.g., dosing coordinator conducting ODS at Visit 2).

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EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Table of Demographic Characteristics

Table 6 - Demographic Characteristics KPI-121-C-011

	KPI-121 0.25% (N=447)	Vehicle (N=454)	Total (N=901)
Age (yrs)			
Mean	57.6	57.3	57.4
SD	15.26	15.53	15.39
Median	59.0	60.0	60.0
Min, Max	18, 89	18, 88	18, 89
Gender, n (%)			
Male	108 (24.2%)	124 (27.3%)	232 (25.7%)
Female	339 (75.8%)	330 (72.7%)	669 (74.3%)
Ethnicity, n (%)			
Hispanic/Latino	112 (25.1%)	97 (21.4%)	209 (23.2%)
Not Hispanic/Latino	335 (74.9%)	357 (78.6%)	692 (76.8%)
Race, n (%)			
American Indian/Alaskan Native	0	1 (0.2%)	1 (0.1%)
Asian	26 (5.8%)	37 (8.1%)	63 (7.0%)
Black/African-American	71 (15.9%)	73 (16.1%)	144 (16.0%)
Native Hawaiian/Other Pacific Islander	0	0	0
White	348 (77.9%)	341 (75.1%)	689 (76.5%)
Unknown	1 (0.2%)	0	1 (0.1%)
Other Race	1 (0.2%)	1 (0.2%)	2 (0.2%)
Multiple	0	1 (0.2%)	1 (0.1%)

ITT = intent-to-treat; Max = maximum value; Min = minimum value; SD = standard deviation

Source: [Table 14.1.4.1](#)

The 901 subjects in the ITT population were predominantly female (74%) and white (77%), with a mean (range) age of 57.4 (18 to 89) years. No meaningful differences were observed between the treatment groups in terms of demographic characteristics.

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NDA 210933 Class 2 resubmission

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Efficacy Results – Primary Endpoints KPI-121-C-011

Table 7 - Summary of Primary Efficacy Results KPI-121-C-011

Primary Endpoint	KPI-121 0.25% (N = 447)		Vehicle (N = 454)		Trt Diff p-value ^a
	Day 1	Change at Day 15	Day 1	Change at Day 15	
Change in ODS scores ^b from Day 1 to Day 15 in ITT Population; mean (SD)	n = 447 74.28 (13.019)	n = 434 -13.58 (19.379)	n = 454 74.13 (12.730)	n = 451 -8.91 (17.579)	-4.67 0.0002
Change in ODS scores ^b from Day 1 to Day 15 in ITT Subgroup with Baseline ODS $\geq$ 68 mm ^c ; mean (SD)	n = 307 80.89 (9.426)	n = 296 -15.59 (20.373)	n = 307 80.54 (9.165)	n = 304 -10.15 (18.739)	-5.44 0.0007

ITT = intent-to-treat; ODS = ocular discomfort severity; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle)

^a P-values were on the difference between KPI-121 and Vehicle by t-test on difference of adjusted least square means on change from baseline score from an analysis of covariance with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model (adjusted mean difference; p-value is 2-sided; significance level is 0.05).

^b ODS scores (from 0 to 100 mm) were derived from data entered into diaries by subjects. Scores were general evaluations across both eyes; there were not separate questions for each eye. Higher scores indicate more severe ocular discomfort. Three-day means were calculated using available data from the 3 days prior to Day 15 (regardless of when Visit 4 [ie, the Day 15 visit] occurred) and the 3 days prior to Day 1. Only available data were used without imputation; if the target number of prior days of diary data was not available, the number of days contributing to the average could be less than the target.

^c The ITT subgroup with more severe baseline ocular discomfort was defined as subjects with ODS score $\geq$ 68 mm 1 day prior to Day 1.

Source: Tables 14.2.1.1 and 14.2.1.2

Statistically significant results favoring KPI-121 0.25% over vehicle were observed for both primary endpoints defined for this study.

The KPI-121 0.25% group had significantly greater improvements than the vehicle group for ODS scores from Day 1 to Day 15 based on 3-day mean scores, in both the overall ITT population ($p = 0.0002$) and the prespecified subgroup of the ITT population with baseline ODS $\geq$ 68 mm ($p = 0.0007$).

Efficacy Results – Secondary Endpoints KPI-121-C-011

Secondary efficacy endpoint comparisons were performed between the KPI-121 0.25% ophthalmic suspension group and the vehicle group following the testing of the primary endpoints. If both of the primary efficacy endpoints achieved statistical significance, the secondary endpoints were to be tested using a hierarchical manner in the following order:

1. Change from baseline (Day 1) in bulbar conjunctival hyperemia scores at the Day 15 visit, in the region of worst severity of bulbar conjunctival hyperemia (as defined at baseline) in the study eye, based on photographic assessment at a central masked photographic reading center.

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2. Change from baseline (Day 1) in investigator-rated bulbar conjunctival hyperemia scores at the Day 15 visit, in the region of worst severity of bulbar conjunctival hyperemia (as defined at baseline based on investigator-rated hyperemia scores) in the study eye.
3. Change in ODS scores calculated as the mean of the scores recorded in the subject's diary for the 3 days prior to Day 8 minus the mean of the scores for the 3 days prior to Day 1.
4. Change from baseline (Day 1) in inferior corneal fluorescein staining scores at the Day 15 visit in the study eye.
5. Change in ODS scores calculated as the mean of the scores recorded in the subject's diary for the 7 days prior to Day 15 minus the mean of the scores for the 7 days prior to Day 1.

All analyses were conducted in the ITT population unless noted otherwise.

Table 8 - Summary of Secondary Efficacy Results KPI-121-C-011

	KPI-121 0.25% (N = 447)	Vehicle (N = 454)	Trt Diff P-value^a
Baseline	n = 440 2.08 (0.635)	n = 452 2.11 (0.612)	-
CFBL at Day 15 Visit	n = 432 -0.35 (0.575)	n = 449 -0.18 (0.546)	-0.18 <0.0001

CCLRU = Cornea and Contact Lens Research Unit; CFBL = change from baseline; ITT = intent-to-treat; SAP = statistical analysis plan; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle)

Note: Conjunctival hyperemia scores (using the CCLRU grading scale, from 0 [none] to 4 [severe]) were based on photographic assessment at a central masked reading center, in the worst region (as defined from evaluations of photographs at Day 1) of the study eye. The study eye was defined using an algorithm described in the SAP.

^a P-values were on the difference between KPI-121 and Vehicle by t-test on difference of adjusted least square means on change from baseline score from an analysis of covariance with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model (adjusted mean difference; p-value is 2-sided; significance level is 0.05).

Source: [Table 14.2.2.1](#)

A statistically significant between-group difference was observed for the secondary endpoint of change from baseline in bulbar conjunctival hyperemia scores in the worst region of the study eye (determined based on Day 1 photographs) at the Day 15 visit, based on photographic assessment conducted at a central masked photographic reading center. The between-group difference was -0.18 favoring KPI-121 0.25% over vehicle ($p < 0.01$). The difference is not considered clinically relevant.

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EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

	KPI-121 0.25% (N = 447)	Vehicle (N = 454)	Trt Diff P-value^a
Baseline	n = 447 2.28 (0.457)	n = 454 2.28 (0.457)	-
CFBL at Day 15 Visit	n = 437 -0.61 (0.646)	n = 453 -0.48 (0.657)	-0.12 0.0036

CCLRU = Cornea and Contact Lens Research Unit; CFBL = change from baseline; ITT = intent-to-treat; SAP = statistical analysis plan; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle)

Note: Conjunctival hyperemia scores were assigned by investigators at the sites, using the CCLRU grading scale, from 0 (none) to 4 (severe). The study eye and the worst region was defined using an algorithm described in the SAP, based upon investigator ratings at Day 1.

^a P-values were on the difference between KPI-121 and Vehicle by t-test on difference of adjusted least square means on change from baseline score from an analysis of covariance with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model (adjusted mean difference; p-value is 2-sided; significance level is 0.05).

Source: [Table 14.2.2.2](#)

A statistically significant between-group difference was observed for the secondary endpoint of change from baseline for investigator-rated conjunctival hyperemia at the Day 15 visit for the worst region of the study eye, as defined based on investigator ratings at the Day 1 visit. The between-group difference was -0.12, favoring KPI-121 0.25% over vehicle ($p < 0.01$). The difference is not considered clinically relevant.

	KPI-121 0.25% (N = 447)	Vehicle (N = 454)	Trt Diff p-value^a
Day 1	n = 447 74.28 (13.019)	n = 454 74.13 (12.730)	-
Change at Day 8	n = 443 -8.05 (15.009)	n = 453 -5.83 (15.176)	-2.18 0.0282

ITT = intent-to-treat; ODS = ocular discomfort severity; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle)

Note: ODS scores (from 0 to 100 mm) were derived from data entered into diaries by subjects. Scores were general evaluations across both eyes; there were not separate questions for each eye. Higher scores indicate more severe ocular discomfort. Three-day means were calculated using available data from the 3 days prior to Day 8 and the 3 days prior to Day 1. Only available data were used without imputation; if the target number of prior days of diary data was not available, the number of days contributing to the average could be less than the target.

^a P-values were on the difference between KPI-121 and Vehicle by t-test on difference of adjusted least square means on change from baseline score from an analysis of covariance with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model (adjusted mean difference; p-value is 2-sided; significance level is 0.05).

Source: [Table 14.2.1.1](#)

A statistically significant between-group difference was observed for the secondary endpoint of change in ODS scores from Day 1 to Day 8 using 3-day means in the ITT population. The between-group difference was -2.18 mm, favoring KPI-121 0.25% over vehicle ($p = 0.03$).

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EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

	KPI-121 0.25% (N = 447)	Vehicle (N = 454)	Trt Diff p-value^a
Baseline	n = 447 2.20 (0.640)	n = 454 2.16 (0.652)	
CFBL at Day 15 Visit	n = 437 -0.53 (0.800)	n = 453 -0.43 (0.739)	-0.08 0.0915

CFBL= change from baseline; ITT = intent-to-treat; NEI = National Eye Institute; SAP = statistical analysis plan; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle)

Note: Inferior corneal staining scores (using the NEI scale, from 0 to 3) in the study eye were based on evaluations by the investigator. The study eye was defined using an algorithm described in the SAP.

^a P-values were on the difference between KPI-121 and Vehicle by t-test on difference of adjusted least square means on change from baseline score from an analysis of covariance with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model (adjusted mean difference; p-value is 2-sided; significance level is 0.05).

Source: Table 14.2.3

A between-group difference of -0.08, favoring KPI-121 0.25% over vehicle, was observed for the secondary endpoint of change from baseline in inferior corneal staining scores at the Day 15 visit (p = 0.09). This difference is not statistically significant.

Based on the hierarchical plan, no further testing of secondary endpoints was permitted after this non-significant difference.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The applicant seeks approval of EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% dosed four times daily (QID) for the temporary relief of the signs and symptoms of dry eye disease. The applicant has conducted one Phase 2 study (Trial KPI-121-C-002) and three Phase 3 studies (Trial KPI-121-C-006, -007, and -011) to support the efficacy and safety of the drug product for this indication.

Each of the 4 studies (Trial KPI-121-C-002, -006, -007 and -011) demonstrated superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary sign endpoint at Day 15. Trials KPI-121-C-006 and -011 demonstrated superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary symptom endpoints. Trial KPI-121-C-002 and Trial KPI-121-C-007 failed to demonstrate superiority of loteprednol etabonate ophthalmic suspension, 0.25% for their primary symptom endpoint, although they both showed numerically favorable results.

Demonstration of superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary symptom endpoints has been duplicated. These data demonstrate substantial evidence of efficacy for KPI-121 0.25% for the temporary relief of the signs and symptoms of dry eye disease.

8. Review of Safety

8.1. Safety Review Approach

The primary evidence of safety reported within this new drug application to support EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is based on integrated data for the safety populations from 4 multicenter, double-masked, randomized, vehicle-controlled dry eye trials (Trials -002, -006, -007, and -011). All trials included KPI-121 0.25% QID and vehicle QID. Trial -002 included a 28-day treatment period, and Trials -006, -007, and -011 included 14-day treatment periods. In all trials, the same formulations of KPI-121 0.25% and vehicle were used.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

For Phase 2 Trial, the treatment period was 28 days and the median duration of exposure to study treatment was 29 days for both treatment groups. For STRIDE 1, STRIDE 2, and STRIDE 3, the treatment periods were 14 days and the median duration of exposure was 15 days for both treatment groups in all 3 trials.

Table 9 - Exposure to Study Treatment (Trials -002, -006, -007, -011)

		Phase 2 Trial 28-day Treatment Period (ITT Population)		STRIDE 1 14-day Treatment Period (Safety Population)		STRIDE 2 14-day Treatment Period (Safety Population)		STRIDE 3 14-day Treatment Period (Safety Population)	
		KPI-121 0.25% QID (N = 73)	Vehicle QID (N = 77)	KPI-121 0.25% QID (N = 459)	Vehicle QID (N = 456)	KPI-121 0.25% QID (N = 452)	Vehicle QID (N = 453)	KPI-121 0.25% QID (N = 449)	Vehicle QID (N = 452)
Exposure (days)	n	73	77	459	456	452	453	449	452
	Mean	28.6	28.6	14.8	14.8	14.8	14.6	14.9	15.7
	SD	1.49	1.59	1.60	1.67	3.80	1.54	3.51	17.38
	Median	29.0	29.0	15.0	15.0	15.0	15.0	15.0	15.0
	Min, Max	20, 35	20, 33	1, 22	8, 25	3, 86	7, 25	1, 75 ^a	1, 383 ^a
1 to 5 days	n (%)	0	0	2 (0.4)	0	3 (0.7)	0	4 (0.9)	1 (0.2)
6 to 10 days	n (%)	0	0	1 (0.2)	4 (0.9)	3 (0.7)	5 (1.1)	7 (1.6)	1 (0.2)
11 to 17 days	n (%)	0	0	443 (96.5)	432 (94.7)	431 (95.4)	436 (96.2)	421 (93.8)	439 (97.1)
> 17 days	n (%)	-	-	13 (2.8)	20 (4.4)	15 (3.3)	12 (2.6)	17 (3.8)	11 (2.4)
18 to 25 days	n (%)	1 (1.4)	1 (1.3)	-	-	-	-	-	-
> 25 days	n (%)	72 (98.6)	76 (98.7)	-	-	-	-	-	-

ITT = intent to treat; Max = maximum; Min = minimum; QID = four times daily; SD = standard deviation

Note: The Phase 2 Trial calculated exposure based on the ITT population, per the statistical analysis plan. The safety population differed from ITT by 1 subject who received a different treatment than they were randomized to receive. There were 72 and 78 subjects, respectively, in the KPI-121 0.25% and vehicle groups in the safety population of the Phase 2 Trial.

^a The maximum values for treatment exposure in the KPI-121 group (75 days) and the vehicle group (383 days) of STRIDE 3 are an artifact of erroneous dates entered into subject diaries. Three subjects entered erroneous dates for their last doses of treatment. Subject (b) (6) in the vehicle group entered (b) (6) (resulting in the appearance of 383 days of exposure). Subject (b) (6) in the KPI-121 group entered (b) (6) instead of (b) (6) (resulting in the appearance of 34 days of exposure). Subject (b) (6) in the KPI-121 group entered (b) (6) instead of (b) (6) (resulting in the appearance of 75 days of exposure). Excluding these data, the maximum exposure in the KPI-121 and vehicle groups was 22 and 30 days, respectively.

Source: Module 5.3.5.1, CSR KPI-121-C-002 (Phase 2), Table 14.1.6; CSR KPI-121-C-006 (STRIDE 1), Table 14.3.7; CSR KPI-121-C-007 (STRIDE 2), Table 14.3.7; CSR KPI-121-C-011 (STRIDE 3), Table 14.3.7

Source: Module 2.7.4

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database:

The safety database is adequate because the application references the Agency's summary findings for another loteprednol ophthalmic product with a concentration which is twice the strength of this product and both products are members of a well-studied class of products, corticosteroids. The effects of corticosteroids on the eye are well established with Warnings and Precautions listed in each of the approved products in this class.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

Adverse events were categorized as ophthalmic and systemic. Analyses were prepared using an integrated safety population for the trials, which was defined as all randomized subjects who received at least 1 dose of study treatment and from whom at least 1 safety assessment was obtained after randomization.

Treatment-emergent adverse events (TEAEs) were defined as those events with onset after the first dose of randomized study treatment or, if occurring prior to first dose, worsened after administration of first dose.

8.3.3. Routine Clinical Tests

Routine ophthalmic examination assessments were conducted on all subjects including visual acuity assessments, slit lamp examination, and dilated fundus examinations in Trials KPI-C-121-002, -006, -007, and -011. Urinalysis, hematology, and serum chemistry were conducted in Trial KPI-121-C-009; vital signs were monitored in Trial KPI-121-C-009.

8.4. Safety Results

8.4.1. Deaths

No deaths have been reported in any clinical trial of EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%.

8.4.2. Serious Adverse Events

Table 10 - Treatment-Emergent Serious Adverse Events (Integrated Safety Population, Trials KPI-121-C-002, KPI-121-C-006, KPI-121-C-007, and KPI-121-C-011)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)
Number (%) of Subjects Reporting Any Serious AE	7 (0.5%)	1 (0.1%)
Injury, Poisoning and Procedural Complications	2 (0.1%)	1 (0.1%)
Eyelid Injury	0	1 (0.1%)
Hip Fracture	1 (0.1%)	0
Joint Dislocation	1 (0.1%)	0
Cardiac Disorders	1 (0.1%)	0
Atrioventricular Block	1 (0.1%)	0
Gastrointestinal Disorders	1 (0.1%)	0
Diverticulum intestinal	1 (0.1%)	0
Hepatobiliary Disorders	1 (0.1%)	0
Cholelithiasis	1 (0.1%)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.1%)	0
Intervertebral Disc Protrusion	1 (0.1%)	0
Psychiatric Disorders	1 (0.1%)	0
Delusional Disorder, Unspecified Type	1 (0.1%)	0
Schizoaffective Disorder	1 (0.1%)	0

AE = adverse event; QID = four times daily

Note: The integrated safety population is the pooled safety populations from the Phase 2 Trial, STRIDE 1, STRIDE 2, and STRIDE 3 (but excluding 3 subjects who participated in STRIDE 3 but had also previously participated in STRIDE 2). At each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

Source: Module 5.3.5.3. [ISS Table 3.5](#)

The treatment-emergent SAEs reported in the KPI-121 0.25% QID group were hip fracture, joint dislocation, atrioventricular block, diverticulum intestinal, cholelithiasis, intervertebral disc protrusion (1 subject each), and delusional disorder and schizoaffective disorder (reported in the same subject).

The frequencies of these reported serious adverse events are consistent expected frequencies of the patient population with dry eye symptoms and are unlikely to be related to use of the drug product.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the 4 dry eye trials, 2871 subjects were randomized, received at least 1 dose of study treatment, and were included in the safety populations. This number includes 3 subjects in STRIDE 3 who had previously participated in STRIDE 2. In the ISS analysis, the data from these subjects' participation in STRIDE 2 are included and the data from their participation in STRIDE 3 are excluded. Thus, the ISS population includes 2868 subjects. Of these, 1430 subjects were treated with KPI-121 0.25% QID and 1438 subjects were treated with vehicle QID. The majority ($\geq 99.0\%$) of subjects completed the trial according to the respective protocol (Table 9). Twenty-eight subjects (1.0%; 28/2868) discontinued the trials early, primarily due to withdrawal by subject or other reason.

Table 11 - Subject Disposition for Trials of Dry Eye Disease (Integrated Safety Population)

	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)	Overall (N = 2868)
Completed Trial	1411 (98.7%)	1429 (99.4%)	2840 (99.0%)
Subjects Withdrawn Early from the Trial	19 (1.3%)	9 (0.6%)	28 (1.0%)
Reason for Early Withdrawal			
Withdrawal by subject	7 (0.5%)	3 (0.2%)	10 (0.3%)
Adverse event	4 (0.3%)	0	4 (0.1%)
Lost to follow-up	2 (0.1%)	2 (0.1%)	4 (0.1%)
Physician decision	0	0	0
Pregnancy	0	0	0
Other	6 (0.4%)	4 (0.3%)	10 (0.3%)

QID = four times daily

Note: The integrated safety population is the pooled safety populations from the Phase 2 Trial, STRIDE 1, STRIDE 2, and STRIDE 3 (but excluding 3 subjects who participated in STRIDE 3 but had also previously participated in STRIDE 2).

Source: Module 5.3.5.3, [ISS Table 1.1.1](#)

Treatment-emergent AEs leading to permanent withdrawal of study treatment were reported in 0.7% (10/1430) and 0.3% (5/1438) of subjects in the KPI-121 0.25% QID and vehicle QID groups, respectively. The AEs leading to permanent withdrawal of subjects in the KPI-121 0.25% QID group were conjunctival hyperemia, conjunctival edema, eye pruritus, ocular hyperemia, hip fracture, palpitations, instillation site pain, cholelithiasis, drug hypersensitivity, blood pressure increased, neck pain, headache, delusional disorder, schizoaffective disorder, dyspnea, and rash (1 subject each).

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AEs leading to permanent withdrawal in the vehicle QID group were corneal infiltrates, eye irritation, vision blurred, herpes zoster, nasopharyngitis, eyelid injury, and nausea (1 subject each).

Table 12 - Number (%) of Subjects Reporting Adverse Events Leading to Permanent Withdrawal of Study Treatment (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)
Number (%) Of Subjects Reporting Any AE Leading To Permanent Withdrawal Of Study Treatment	10 (0.7%)	5 (0.3%)
Eye Disorders	2 (0.1%)	2 (0.1%)
Conjunctival Hyperaemia	1 (0.1%)	0
Conjunctival Oedema	1 (0.1%)	0
Corneal Infiltrates	0	1 (0.1%)
Eye Irritation	0	1 (0.1%)
Eye Pruritus	1 (0.1%)	0
Ocular Hyperaemia	1 (0.1%)	0
Vision Blurred	0	1 (0.1%)
Infections and Infestations	0	2 (0.1%)
Herpes Zoster	0	1 (0.1%)
Nasopharyngitis	0	1 (0.1%)
Injury, Poisoning and Procedural Complications	1 (0.1%)	1 (0.1%)
Eyelid Injury	0	1 (0.1%)
Hip Fracture	1 (0.1%)	0
Cardiac Disorders	1 (0.1%)	0
Palpitations	1 (0.1%)	0
Gastrointestinal Disorders	0	1 (0.1%)
Nausea	0	1 (0.1%)
General Disorders and Administration Site Conditions	1 (0.1%)	0
Instillation Site Pain	1 (0.1%)	0
Hepatobiliary Disorders	1 (0.1%)	0
Cholelithiasis	1 (0.1%)	0
Immune System Disorders	1 (0.1%)	0
Drug Hypersensitivity	1 (0.1%)	0
Investigations	1 (0.1%)	0
Blood Pressure Increased	1 (0.1%)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.1%)	0
Neck Pain	1 (0.1%)	0

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System Organ Class Preferred Term	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)
Nervous System Disorders	1 (0.1%)	0
Headache	1 (0.1%)	0
Psychiatric Disorders	1 (0.1%)	0
Delusional Disorder, Unspecified Type	1 (0.1%)	0
Schizoaffective Disorder	1 (0.1%)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1%)	0
Dyspnoea	1 (0.1%)	0
Skin and Subcutaneous Tissue Disorders	1 (0.1%)	0
Rash	1 (0.1%)	0

AE = adverse event; QID = four times daily

Note: The integrated safety population is the pooled safety populations from the Phase 2 Trial, STRIDE 1, STRIDE 2, and STRIDE 3 (but excluding 3 subjects who participated in STRIDE 3 but had also previously participated in STRIDE 2). At each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

Source: Module 5.3.5.3, [ISS Table 3.6](#)

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

AEs were reported by 13% (185/1430) and 10% (150/1438) of subjects in the KPI-121 0.25% QID and vehicle QID groups, respectively. The most frequently reported preferred term was instillation site pain, which was reported by 5% of subjects in the KPI-121 0.25% QID group and 4% of subjects in the vehicle QID group. All other AEs were reported by $\leq 0.7\%$ of subjects in the KPI-121 0.25% QID group.

Instillation site pain is listed as the most frequently reported adverse drug reaction in clinical trials of KPI-121 0.25% in dry eye disease in the following table.

Table 13 - Number (%) of Subjects Reporting Common ($\geq 1\%$ in Either Treatment Group) Adverse Events (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)
Number (%) of Subjects Reporting Any AE ^a	185 (12.9%)	150 (10.4%)
General Disorders and Administration Site Conditions ^a	82 (5.7%)	69 (4.8%)
Instillation Site Pain	74 (5.2%)	63 (4.4%)

AE = adverse event; PT = preferred term; QID = four times daily; SOC = system organ class

Note: The integrated safety population is the pooled safety populations from the Phase 2 Trial, STRIDE 1, STRIDE 2, and STRIDE 3 (but excluding 3 subjects who participated in STRIDE 3 but had also previously participated in STRIDE 2). At each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

^a The numbers and percentages for overall AEs and AEs by SOC are inclusive of all PTs. PTs are only included in the table if $\geq 1\%$ of subjects in either treatment group reported that AE.

Source: Module 5.3.5.3, [ISS Table 3.2.1](#)

Table 14 - Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Either Treatment Group (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% QID (N=1430)	Vehicle (N=1438)
Number (%) of Subjects Reporting Any AE	185 (12.9%)	150 (10.4%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	82 (5.7%)	69 (4.8%)
INSTILLATION SITE PAIN	74 (5.2%)	63 (4.4%)
INSTILLATION SITE PRURITUS	3 (0.2%)	5 (0.3%)
INSTILLATION SITE DISCHARGE	2 (0.1%)	0
INSTILLATION SITE FOREIGN BODY SENSATION	2 (0.1%)	0
INSTILLATION SITE REACTION	1 (0.1%)	1 (0.1%)
CHEST PAIN	1 (0.1%)	0
INSTILLATION SITE DISCOMFORT	0	1 (0.1%)
INSTILLATION SITE ERYTHEMA	0	1 (0.1%)
INSTILLATION SITE IRRITATION	1 (0.1%)	0
INSTILLATION SITE LACRIMATION	1 (0.1%)	0
PAIN	1 (0.1%)	0
PYREXIA	0	1 (0.1%)
EYE DISORDERS	50 (3.5%)	67 (4.7%)
EYE IRRITATION	10 (0.7%)	13 (0.9%)
EYE PRURITUS	6 (0.4%)	12 (0.8%)
VISION BLURRED	5 (0.3%)	8 (0.6%)
CONJUNCTIVAL HYPERAEMIA	4 (0.3%)	7 (0.5%)
EYE PAIN	5 (0.3%)	5 (0.3%)
FOREIGN BODY SENSATION IN EYES	3 (0.2%)	5 (0.3%)
DRY EYE	1 (0.1%)	5 (0.3%)
LACRIMATION INCREASED	3 (0.2%)	3 (0.2%)
EYE DISCHARGE	2 (0.1%)	3 (0.2%)
PHOTOPHOBIA	3 (0.2%)	2 (0.1%)
BLEPHARITIS	3 (0.2%)	1 (0.1%)
CONJUNCTIVAL HAEMORRHAGE	1 (0.1%)	3 (0.2%)

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System Organ Class Preferred Term	KPI-121 0.25% QID (N=1430)	Vehicle (N=1438)
EYELID MARGIN CRUSTING	1 (0.1%)	2 (0.1%)
BLEPHAROSPASM	0	2 (0.1%)
CONJUNCTIVAL VASCULAR DISORDER	1 (0.1%)	1 (0.1%)
CONJUNCTIVITIS ALLERGIC	1 (0.1%)	1 (0.1%)
CORNEAL INFILTRATES	1 (0.1%)	1 (0.1%)
EYELIDS PRURITUS	1 (0.1%)	1 (0.1%)
KERATITIS	1 (0.1%)	1 (0.1%)
OCULAR HYPERAEMIA	1 (0.1%)	1 (0.1%)
TRICHIASIS	1 (0.1%)	1 (0.1%)
VISUAL IMPAIRMENT	1 (0.1%)	1 (0.1%)
CATARACT	0	1 (0.1%)
CONJUNCTIVAL OEDEMA	1 (0.1%)	0
EYELID PAIN	0	1 (0.1%)
EYELID PTOSIS	1 (0.1%)	0
GROWTH OF EYELASHES	0	1 (0.1%)
IRITIS	1 (0.1%)	0
OCULAR DISCOMFORT	0	1 (0.1%)
OCULAR HYPERTENSION	1 (0.1%)	0
PUNCTATE KERATITIS	0	1 (0.1%)
SCLERAL HYPERAEMIA	1 (0.1%)	0
VISUAL ACUITY REDUCED	1 (0.1%)	0
VITREOUS DETACHMENT	1 (0.1%)	0
VITREOUS FLOATERS	0	1 (0.1%)
INFECTIONS AND INFESTATIONS	11 (0.8%)	19 (1.3%)
UPPER RESPIRATORY TRACT INFECTION	2 (0.1%)	4 (0.3%)
BRONCHITIS	1 (0.1%)	2 (0.1%)
NASOPHARYNGITIS	0	3 (0.2%)
SINUSITIS	1 (0.1%)	2 (0.1%)
HERPES ZOSTER	1 (0.1%)	1 (0.1%)
URINARY TRACT INFECTION	1 (0.1%)	1 (0.1%)
BODY TINEA	0	1 (0.1%)
CONJUNCTIVITIS	0	1 (0.1%)
EAR INFECTION	1 (0.1%)	0
INFLUENZA	0	1 (0.1%)
LOWER RESPIRATORY TRACT INFECTION	0	1 (0.1%)
PNEUMONIA	1 (0.1%)	0
RHINITIS	1 (0.1%)	0
STREPTOCOCCAL INFECTION	1 (0.1%)	0
TOOTH INFECTION	1 (0.1%)	0
VAGINAL INFECTION	0	1 (0.1%)
VIRAL INFECTION	0	1 (0.1%)
NERVOUS SYSTEM DISORDERS	10 (0.7%)	7 (0.5%)
HEADACHE	5 (0.3%)	4 (0.3%)
SINUS HEADACHE	2 (0.1%)	1 (0.1%)
DIZZINESS	1 (0.1%)	1 (0.1%)
HYPOAESTHESIA	1 (0.1%)	0
MIGRAINE	1 (0.1%)	0
NERVE COMPRESSION	1 (0.1%)	0
OPHTHALMOPLGIC MIGRAINE	0	1 (0.1%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (0.8%)	4 (0.3%)
LIGAMENT SPRAIN	2 (0.1%)	1 (0.1%)
EYELID INJURY	1 (0.1%)	1 (0.1%)
JOINT INJURY	1 (0.1%)	1 (0.1%)
ARTHROPOD BITE	1 (0.1%)	0
CONTUSION	1 (0.1%)	0

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System Organ Class Preferred Term	KPI-121 0.25% QID (N=1430)	Vehicle (N=1438)
FALL	0	1 (0.1%)
FOREIGN BODY IN EYE	1 (0.1%)	0
HIP FRACTURE	1 (0.1%)	0
JOINT DISLOCATION	1 (0.1%)	0
LIGAMENT RUPTURE	1 (0.1%)	0
PROCEDURAL PAIN	1 (0.1%)	0
GASTROINTESTINAL DISORDERS	9 (0.6%)	2 (0.1%)
TOOTHACHE	3 (0.2%)	0
NAUSEA	1 (0.1%)	1 (0.1%)
ABDOMINAL PAIN	1 (0.1%)	0
ABDOMINAL PAIN UPPER	1 (0.1%)	0
CONSTIPATION	1 (0.1%)	0
DIVERTICULUM INTESTINAL	1 (0.1%)	0
GASTROESOPHAGEAL REFLUX DISEASE	1 (0.1%)	0
GINGIVAL BLEEDING	0	1 (0.1%)
HYPOAESTHESIA ORAL	1 (0.1%)	0
ESOPHAGEAL RUPTURE	1 (0.1%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (0.4%)	5 (0.3%)
NASAL CONGESTION	2 (0.1%)	1 (0.1%)
DYSPHONIA	0	1 (0.1%)
DYSPNOEA	1 (0.1%)	0
OROPHARYNGEAL PAIN	1 (0.1%)	0
PARANASAL SINUS HYPERSECRETION	0	1 (0.1%)
PULMONARY CONGESTION	0	1 (0.1%)
RHINORRHOEA	1 (0.1%)	0
SINUS CONGESTION	1 (0.1%)	0
SNEEZING	0	1 (0.1%)

System Organ Class Preferred Term	KPI-121 0.25% QID (N=1430)	Vehicle (N=1438)
INVESTIGATIONS	7 (0.5%)	2 (0.1%)
INTRAOCULAR PRESSURE INCREASED	5 (0.3%)	2 (0.1%)
BLOOD PRESSURE INCREASED	2 (0.1%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (0.3%)	4 (0.3%)
RASH	2 (0.1%)	1 (0.1%)
ECCHYMOSIS	1 (0.1%)	1 (0.1%)
DERMATITIS CONTACT	1 (0.1%)	0
PRURITUS	0	1 (0.1%)
RASH ERYTHEMATOUS	0	1 (0.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	6 (0.4%)	1 (0.1%)
NECK PAIN	2 (0.1%)	0
INTERVERTEBRAL DISC PROTRUSION	1 (0.1%)	0
OSTEOARTHRITIS	0	1 (0.1%)
OSTEOPOROSIS	1 (0.1%)	0
PAIN IN EXTREMITY	1 (0.1%)	0
SPINAL COLUMN STENOSIS	1 (0.1%)	0
CARDIAC DISORDERS	2 (0.1%)	0
ATRIOVENTRICULAR BLOCK	1 (0.1%)	0
PALPITATIONS	1 (0.1%)	0
EAR AND LABYRINTH DISORDERS	2 (0.1%)	0
EAR PAIN	1 (0.1%)	0
VERTIGO	1 (0.1%)	0

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System Organ Class Preferred Term	KPI-121 0.25% QID (N=1430)	Vehicle (N=1438)
IMMUNE SYSTEM DISORDERS	2 (0.1%)	0
DRUG HYPERSENSITIVITY	1 (0.1%)	0
HYPERSENSITIVITY	1 (0.1%)	0
PSYCHIATRIC DISORDERS	1 (0.1%)	1 (0.1%)
ANXIETY	0	1 (0.1%)
DELUSIONAL DISORDER, UNSPECIFIED TYPE	1 (0.1%)	0
SCHIZOAFFECTIVE DISORDER	1 (0.1%)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.1%)	0
ANAEMIA	1 (0.1%)	0
ENDOCRINE DISORDERS	0	1 (0.1%)
HYPOTHYROIDISM	0	1 (0.1%)
HEPATOBIILIARY DISORDERS	1 (0.1%)	0
CHOLELITHIASIS	1 (0.1%)	0
RENAL AND URINARY DISORDERS	1 (0.1%)	0
NEPHROLITHIASIS	1 (0.1%)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.1%)	0
PELVIC FLUID COLLECTION	1 (0.1%)	0
VASCULAR DISORDERS	1 (0.1%)	0
HYPERTENSION	1 (0.1%)	0

Note: At each level of summarization, subjects reporting more than one event are only counted once.

Note: Within System Organ Class, Preferred Terms are presented by descending incidence overall.

Note: Adverse events coded using MedDRA Version 19.0

Note: N = number of subjects in the Safety population.

Source datasets: ADSL, ADAE

Program: t-teae.sas

Date/Time of Run: 10APR2020:12:14

8.4.5. Laboratory Findings

Urinalysis, hematology, and serum chemistry were conducted in Trial KPI-121-C-009, a single-center, open-label trial designed to evaluate the systemic pharmacokinetics and safety of KPI-121 0.25% QID in healthy adult subjects. No significant effects were noted.

8.4.6. Vital Signs

Vital signs were monitored in Trial KPI-121-C-009, a single-center, open-label trial designed to evaluate the systemic pharmacokinetics and safety of KPI-121 0.25% QID in healthy adult subjects. There was no significant effect.

8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were conducted in Trial KPI-121-C-009, a single-center, open-label trial designed to evaluate the systemic pharmacokinetics and safety of KPI-121 0.25% QID in healthy adult subjects. The electrocardiograms revealed no significant effect.

8.4.8. QT

QT studies were not performed during the clinical development of loteprednol etabonate ophthalmic suspension, 0.25%.

8.5. Safety Analyses by Demographic Subgroups

Pooled subgroup analyses were performed for all AEs by age group (< 65 and ≥ 65 years) and gender (male and female). There was no trend in the ISS data to indicate any difference in the safety profile of KPI-121 0.25% for the subgroups defined by age or gender.

8.6. Specific Safety Studies/Clinical Trials

The applicant did not perform assessment of corneal endothelial cell counts. The adverse event profile of loteprednol etabonate ophthalmic suspension is well-known. This is acceptable.

8.7. Additional Safety Explorations

8.7.1. Human Reproduction and Pregnancy

There are no adequate and well controlled studies with loteprednol etabonate in pregnant women.

8.7.2. Pediatrics and Assessment of Effects on Growth

This application was presented at the Pediatric Review Committee on March 13, 2019, with the proposed Indication of temporary relief of the signs and symptoms of dry eye disease. This application triggers PREA as a new indication. The applicant requested full waiver for pediatrics birth to less than 17 years of age because studies are impossible or highly impracticable. The PeRC agreed with the request for full waiver as presented in the Agreed iPSP.

8.7.3. Intraocular Pressure

Corticosteroids are well known to elevate intraocular pressure in certain patients (likely due to genetic predisposition). This risk is described in the labeling of all ophthalmic corticosteroids, although it is more of a concern if the product were to be used for more than 14 days.

	Study Eye		Fellow Eye	
	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)	KPI-121 0.25% QID (N = 1430)	Vehicle QID (N = 1438)
> 5 mmHg increase from BL	30 (2.1%)	22 (1.5%)	33 (2.3%)	20 (1.4%)
> 5 mmHg increase from BL and ≥ 21 mmHg measurement	9 (0.6%)	3 (0.2%)	8 (0.6%)	4 (0.3%)
≥ 10 mmHg increase from BL	4 (0.3%)	0	3 (0.2%)	1 (0.1%)
≥ 10 mmHg increase from BL and ≥ 21 mmHg measurement	3 (0.2%)	0	2 (0.1%)	1 (0.1%)

BL = baseline; QID = four times daily

Source: Module 5.3.5.3, ISS Table 5.2.1 and 5.2.2

8.7.1. Safety Update

The 120-day safety update was submitted on September 2, 2020. Following the resubmission of NDA 210933 on 30 April 2020, there have been no additional or ongoing trials with KPI-121 0.25%; per the applicant there is no new safety information that would affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

At the time of this submission, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% has not been marketed in any region globally. Therefore, no postmarketing data are available on this specific product.

8.8.2. Expectations on Safety in the Postmarket Setting

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Labeling Recommendations

NDA 210933 EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is recommended for approval with the labeling attached at the end of this review.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

13.2. Financial Disclosure

See the Medical Officer review dated July 29, 2019, in DARRTS for the financial disclosure information for covered studies KPI-121-C-002, -006, and -007.

Covered Clinical Study (Name and/or Number): KPI-121-C-011

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>82 principle investigators</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>82 principal</u>		

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<u>investigators</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

15 Page(s) have been Withheld in Full immediately following this page. Please refer to the Final Labeling Section.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
10/26/2020 02:30:55 PM

WILEY A CHAMBERS
10/26/2020 02:50:37 PM

Deputy Division Director
and Cross-Discipline Team Leader Review of NDA 210933

Date	8/6/19
From	Wiley A. Chambers, M.D. and William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review and Division Director Review
NDA#	NDA 210933
Applicant	Kala Pharmaceuticals, Inc.
Date of Submission	10/15/2018
PDUFA Goal Date	8/15/2019
Proprietary Name	EYSUVIS
Established Name	loteprednol etabonate ophthalmic suspension, 0.25%
Dosage Form	ophthalmic suspension
Indication	temporary relief of the signs and symptoms of dry eye disease
Dosing Regimen	Instill one to two drops into each eye four times daily for two weeks
Regulatory Action	Complete Response will be issued

1. Introduction/Benefit-Risk Assessment

This is a 505(b)(2) new drug application for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%. The reference listed drug is LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, NDA 020583. The Applicant's bridge consists of chemical identity, and comparative nonclinical pharmacokinetics (PK). In this review, EYSUVIS may also be referred to as KPI-121 0.25%.

Benefit-Risk Assessment Framework

Studies -002, --006 and -007 demonstrated superiority of EYSUVIUS to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15. However, only -006 demonstrated superiority of EYSUVIS to the vehicle for the primary symptom endpoint; -002 and -007 failed to demonstrate superiority. While study -002 may have been underpowered to demonstrate a difference in a symptom, an additional trial should be conducted prior to accepting the results from KPI-121-C-006. The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of EYSUVIS for ten days can be monitored with slit lamp and fundus examinations.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The health and function of the cornea is dependent on a thin tear film layer made up of an aqueous, mucin, lipids, lysozymes, immunoglobulins, glucose, and salts. In keratoconjunctivitis sicca (dry eye), one or more of the components is deficient.	Keratoconjunctivitis sicca (dry eye) is a potentially debilitating condition which can impede the activities of daily living and can be associated with anterior segment damage to the eye.
Current Treatment Options	Currently available treatments for keratoconjunctivitis sicca (dry eye) include the use of OTC demulcents, Rx topical calcineurin inhibitors (cyclosporine ophthalmic emulsion and cyclosporine ophthalmic solution), and/or a lymphocyte function-associated antigen-1 (LFA-1) antagonist.	This product, if approved, would provide an alternative product to temporarily treat the signs and symptoms of dry eye disease.
Benefit	Three studies demonstrated superiority of EYSUVIS to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15, however, only one of these studies demonstrated superiority of EYSUVIS to the vehicle for the primary symptom endpoint.	An additional trial is recommended to support the sign and symptom results from KPI-121-C-006.
Risk and Risk Management	Serious adverse reactions associated with ophthalmic corticosteroids include elevated IOP, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.	The potential serious adverse events associated with the use of topical ophthalmic corticosteroids can be managed with limitations on dosing for ten days and monitoring with slit lamp examinations.

2. Background

Keratoconjunctivitis sicca (KCS), commonly referred to as dry eye, is a disease affecting the ocular surface, the tear film, and related ocular tissues and organs. The ocular surface is supported and maintained by the tear film, which is composed of 3 distinct components (lipid, aqueous, and mucin) that make up 2 fluid layers. Meibomian glands along the upper and lower lid margins produce the outer lipid layer of the tear film. The inner layer, an aqueous and mucin mixture, is composed of aqueous fluid produced by the main and accessory lacrimal glands and mucins produced by goblet cells on the conjunctival epithelium as well as corneal epithelial cells.

Safety and efficacy for the treatment of dry eye disease indication is recommended to be demonstrated in adequate and well-controlled, independent trials. A demonstration of a statistically significant difference between the test treatment and vehicle for at least one objective sign and at least one subjective symptom of dry eye is expected. Increases of ≥ 10 mm in Schirmer wetting from baseline have been validated (i.e., qualified) as being clinically relevant based on correlation with decreased corneal staining.

Table 1 - FDA Approved Treatments

Indication:	To increase tear production	
Restasis	cyclosporine ophthalmic emulsion	NDA 50-790
Cequa	cyclosporine ophthalmic solution	NDA 210913
Indication:	To treat signs and symptoms of dry eye disease	
Xiidra	lifitegrast ophthalmic solution	NDA 208073

Current management of dry eye disease often begins with artificial tear replacement and other palliative treatments such as punctal occlusion.

Loteprednol etabonate is a corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated intraocular pressure (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis. Topical ophthalmic corticosteroid products are approved for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies. Kala believes a significant unmet need exists for a safe and effective corticosteroid product to provide reliable temporary relief of the signs and symptoms of dry eye. The applicant has proposed a two-week dosing to potentially address the known ocular adverse event profile of corticosteroids. Topical ophthalmic corticosteroid products have typically included a Warning

about the need for additional monitoring, if the product is used for more than 10 days.

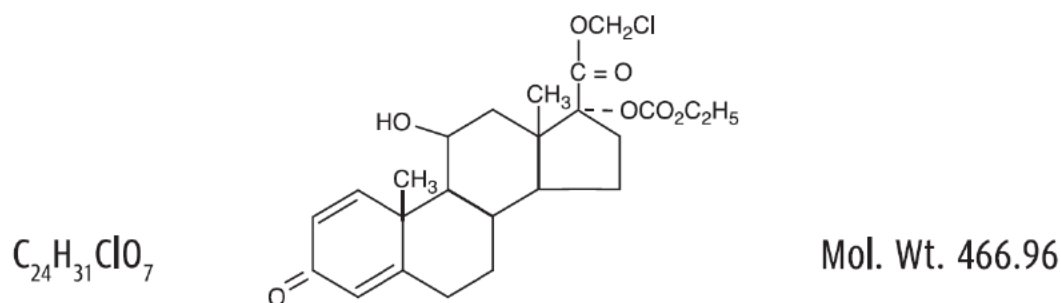
3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Section 6.1.1, 6.2.1 and 6.3.1 and Sections 6.1.2, 6.2.2, and 6.3.2
☒	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

4. Product Quality

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is a sterile aqueous suspension of loteprednol etabonate (LE) for topical ophthalmic use. Each milliliter contains 2.5 mg LE as the active ingredient. Loteprednol etabonate is represented by the following structural formula:



The quantitative composition and function of each component in EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is listed in the following table. (b) (4)

Table 2 - Composition of EYSUVIS 0.25%

Ingredient	Quality Standard	Function	Amount (mg) in each mL of EYSUVIS 0.25%	Concentration (%w/v) in EYSUVIS 0.25%
Loteprednol etabonate	(b) (4)	Active Pharmaceutical Ingredient	2.5	0.25
Glycerin	USP-NF	(b) (4)	(b) (4)	
Sodium citrate, dihydrate	USP-NF			
Sodium chloride	USP-NF			
Poloxamer 407	USP-NF			
Edetate disodium, dihydrate	USP-NF			
Citric acid, (b) (4)	USP-NF	Preservative	0.1	0.01
Benzalkonium chloride	USP-NF			
Water for injection	USP-NF			

USP-NF: United States Pharmacopeia - National Formulary

Source: Module 2.3.P

Table 3 - Quality control specifications for release of EYSUVIS 0.25% commercial fill bottles

Attribute and Test	Method Number	Acceptance Criteria
Appearance	(b) (4) Visual Observation	White dropper bottle (b) (4)
pH	(b) (4)	
Osmolality		
Benzalkonium Chloride Assay		
Particle Size		
Minimum Fill Volume	USP<755>	(b) (4)
Identity	(b) (4)	
Loteprednol Etabonate (LE)		
Assay Loteprednol Etabonate		
Loteprednol Etabonate related impurities ¹		
A. Loteprednol Etabonate related substances and impurities B. Total of all related impurities		
EDTA Assay	(b) (4)	
Sterility		
	USP<71>	Meets USP test requirements

NMT = Not More Than; (b) (4) EDTA = edetate disodium, dihydrate

(b) (4)

Source: Module 2.3.P

The container closure system for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% consists of a white low-density polyethylene (LDPE) plastic bottle with nominal capacity of 10 mL; a controlled-drop, linear LDPE (LLDPE) tip; and a pink high-density polyethylene (HDPE) 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.

From the Product Quality review dated 2/22/2109:

Facilities Inspections

The Office of Process and Facilities issued an overall acceptable recommendation for all the facilities on 1/31/2019.

Drug Substance Manufacturer(s)

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)			History of VAI and NAI inspections. No API related recalls.	Acceptable based on inspectional history review with lack of quality defect signals.

Drug Product Manufacturer(s)

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Assessment	Final Recommendation
(b) (4)			History of VAI and NAI inspections. No drug product related recalls.	Acceptable based on inspectional history review.
			- New dosage form for the facility. - History of NAI inspections.	Acceptable based on inspectional history review.

(b) (4)	History of NAI inspections.	Acceptable based on inspectional history review.
	History of VAI and NAI inspections.	Acceptable based on inspectional history review.
	History of NAI inspections.	Acceptable based on inspectional history review.
	History of NAI inspections.	Acceptable based on inspectional history review.
	History of VAI and NAI inspections.	Acceptable based on inspectional history review.
	History of VAI and NAI inspections.	Acceptable based on inspectional history review.

5. Nonclinical Pharmacology/Toxicology

Loteprednol etabonate (LE) is a corticosteroid ester initially approved in 1998 (Bausch & Lomb's NDA 20-583 for LOTEMAX). From a nonclinical perspective, the NDA relies on Kala's own studies, and FDA's finding of safety for the approved listed drug LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 20-583. The nonclinical Pharmacology/Toxicology (P/T) review identified no new safety concerns for EYSUVIS.

6. Clinical Pharmacology

Study KPI-121-C-009 characterized the PK exposure of LE in 20 healthy adult subjects. Plasma concentrations of LE, and the inactive metabolites, PJ-90 and PJ-91, were analyzed using a validated LC/MS/MS method. The analytical ranges of the assay were validated from 1.00 to 1,000 ng/mL for LE and PJ-91 and the lower limit of assay quantitation (LLOQ) was 1.00 ng/mL. The analytical ranges of the assay were validated from 5.00 to 5,000 ng/mL for PJ-90 and the LLOQ was 5.00 ng/mL.

All plasma concentrations of LE, PJ-90, and PJ-91 at every time point pre-and post-instillation of 2 drops of EYSUVIS 0.25% in each eye QID for 15 days were BLQ (Below the Limit of Quantitation). Thus, the Applicant was unable to characterize the PK parameters for LE, PJ-90, and PJ-91.

7. Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

8. Clinical/Statistical- Efficacy

From the Clinical review dated 7/30/2019:

The primary evidence of efficacy reported within this new drug application to support EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% for the temporary relief of the signs and symptoms of dry eye disease is based on data from 3 multicenter, double-masked, randomized, vehicle-controlled dry eye trials (Trials KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007). All 3 dry eye trials included 2 treatment groups: KPI-121 0.25% QID and vehicle QID. Trial KPI-121-C-002 included a 28-day treatment period, and Trials KPI-121-C-006 and KPI-121-C-007 included 14-day treatment periods. In all 3 trials, a run-in period preceded the treatment period wherein all subjects applied KPI-121 vehicle QID for 2 weeks.

In all trials, the same formulations of KPI-121 0.25% and vehicle were used.

Efficacy Results – Primary Endpoints KPI-121-C-002

Table 4 - Summary of Mean Bulbar Conjunctival Hyperemia Scores of the Worst Region as Determined by Photographic Assessment in the Study Eye (ITT Population) KPI-121-C-002

	KPI-121 0.25% (N = 73)	Vehicle (N = 77)	Between-group Difference p-value ^a
Day 1 (Baseline)			
n	73	77	
Mean (SD)	2.18 (0.452)	2.05 (0.426)	
Median	2.00	2.00	
Day 15 (Observed) ^b			
N	73	77	
Mean (SD)	1.52 (0.580)	1.71 (0.686)	-0.26 0.0090 ^c
Median	2.00	2.00	
Min, Max	0, 3	0, 3	
Day 15 (Change From Baseline) ^b			
N	73	77	
Mean (SD)	-0.66 (0.583)	-0.34 (0.661)	-0.26 0.0090 ^d
Median	-1.00	0.00	
Min, Max	-2, 0	-2, 1	
Day 29 (Observed)			
N	72	77	
Mean (SD)	1.44 (0.669)	1.61 (0.588)	-0.21 0.0387 ^c
Median	1.00	2.00	
Min, Max	0, 3	0, 3	
Day 29 (Change From Baseline)			
N	72	77	
Mean (SD)	-0.74 (0.692)	-0.44 (0.639)	-0.21 0.0387 ^d
Median	-1.00	0.00	
Min, Max	-2, 1	-2, 1	

Note: Worst region (nasal, temporal, or central) was defined based on baseline evaluations. Day 29 is the primary timepoint.

^a P-values are 2-sided; significance level is 0.05. Between-group differences are for KPI-121 minus vehicle, where negative values favor KPI-121.

^b Day 15 was evaluated as a secondary endpoint (see Section 11.2.1), but is presented alongside the results for the primary endpoint (Day 29) to provide a complete summary of mean bulbar conjunctival hyperemia scores of the worst region as determined by photographic assessment in the study eye at both timepoints.

^c P-values are on the differences between KPI-121 and vehicle by t-test on difference of adjusted least square means on observed score from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

^d P-values are on the difference between KPI-121 and vehicle by t-test on difference of adjusted least square means on change from baseline from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

Source: Tables 14.2.1.1.1 and 14.2.1.1.2

At Day 29 (primary timepoint), the mean bulbar conjunctival hyperemia score as determined by photographic assessment of the worst region (determined at baseline) of the study eye was 1.4 in the KPI-121 0.25% group compared with 1.6 in the vehicle group. The between-group difference was statistically significant, favoring KPI-121 0.25% over vehicle (p = 0.039).

Table 5 -Summary of Modified SANDE Severity Scores for the 7-day Average Prior to Visit (ITT Population) KPI-121-C-002

	KPI-121 0.25% (N = 73)	Vehicle (N = 77)	Between-group Difference p-value ^a
Baseline ^b			
n	73	77	
Mean (SD)	66.82 (15.126)	67.63 (13.321)	
Median	67.43	68.14	
Min, Max	12, 94	30, 96	
Day 15 (Observed) ^b			
N	72	77	
Mean (SD)	58.83 (20.745)	63.63 (17.844)	-4.12 0.1072 ^c
Median	63.00	65.43	
Min, Max	2, 95	6, 98	
Day 15 (Change From Baseline) ^b			
N	72	77	
Mean (SD)	-7.96 (17.344)	-3.99 (13.591)	-4.12 0.1072 ^d
Median	-3.14	-2.00	
Min, Max	-78, 28	-61, 26	
Day 29 (Observed)			
N	73	77	
Mean (SD)	57.05 (23.892)	60.47 (19.770)	-2.64 0.3764 ^c
Median	63.71	60.14	
Min, Max	3, 97	6, 97	
Day 29 (Change From Baseline)			
N	73	77	
Mean (SD)	-9.77 (21.422)	-7.16 (14.512)	-2.64 0.3764 ^d
Median	-6.43	-5.86	
Min, Max	-71, 26	-63, 27	

Note: Modified SANDE Severity Scores were calculated based on the average 7-day score prior to the visit. Day 29 is the primary timepoint.

^a P-values are 2 sided; significance level is 0.05. Between-group differences are for KPI-121 minus vehicle, where negative values favor KPI-121.

^b Day 15 was evaluated as a secondary endpoint (see Section 11.2.8), but is presented alongside the results for the primary endpoint (Day 29) to provide a complete summary of Modified SANDE Severity scores at both timepoints.

^c P-values are on the difference between KPI-121 and vehicle by t-test on difference of adjusted square means square on observed value from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

^d P-values are on the difference between KPI-121 and vehicle by t-test on difference of adjusted square means square on change from baseline from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

Source: Tables 14.2.3.1 and 14.2.3.2

For Modified SANDE Severity Scores, using the mean of scores over the 7 days prior to the Day 29 visit, the results were numerically better in the KPI-121 0.25% group (57.1 mm) compared with the vehicle group (60.5 mm), but they were not statistically significant (p = 0.38).

Efficacy Results – Primary Endpoints KPI-121-C-006

Table 4 - Summary of Primary Efficacy Results KPI-121-C-006

Primary Endpoint (Population)	KPI-121 0.25% (N = 459)		Vehicle (N = 456)		Trt Diff p-value ^a
	Day 1	Change at Day 15	Day 1	Change at Day 15	
Ocular signs					
Conjunctival hyperemia scores ^b at the Day 15 visit (ITT, mean [SD])	n = 458 1.9651 (0.60168)	n = 452 -0.4049 (0.65062)	n = 455 1.9692 (0.61831)	n = 451 -0.1574 (0.60704)	-0.25 < 0.0001
Inferior corneal staining scores ^c at the Day 15 visit (ITT, mean [SD])	n = 459 2.1 (0.70)	n = 455 -0.5 (0.84)	n = 455 2.1 (0.66)	n = 452 -0.4 (0.79)	-0.08 0.1128
Ocular symptoms					
ODS scores ^d at Day 15 (ITT, mean [SD])	n = 459 68.93 (15.888)	n = 455 -14.53 (20.636)	n = 456 69.26 (15.378)	n = 452 -9.16 (17.924)	-5.43 < 0.0001
ODS scores ^d at Day 15 (ITT subgroup with ODS scores ≥68 mm 1 day prior to Day 1, mean [SD])	n = 260 79.38 (10.062)	n = 257 -16.67 (21.937)	n = 264 79.26 (9.741)	n = 264 -10.76 (18.037)	-5.90 0.0009

ITT = intent to treat; ODS = ocular discomfort severity; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle) using least-square means

^a P-values were calculated based on an analysis of covariance with baseline value as covariate and treatment group and randomization strata as fixed effects.

^b Conjunctival hyperemia scores (using the CCLRU grading scale, from 0 [none] to 4 [severe]) were based on masked photographic assessments conducted at a central photographic reading center, in the worst region of the study eye. The study eye and the worst region were defined using an algorithm described in the statistical analysis plan.

^c Inferior corneal staining scores (using the NEI scale, from 0 to 3) in the study eye were based on evaluations by the investigator. The study eye was defined using an algorithm described in the statistical analysis plan.

^d ODS scores (from 0 to 100 mm) were derived from data entered into diaries by subjects. Scores were general evaluations across both eyes; there were not separate questions for each eye. Higher scores indicate more severe ocular discomfort. Three-day means were calculated using available data from the 3 days prior to Day 15 (regardless of when Visit 4 [ie, the Day 15 visit] occurred) and the 3 days prior to Day 1. Only available data are used without imputation; if the target number of prior days of diary data was not available, the number of days contributing to the average could be less than the target.

Source: Tables 14.2.1.1, 14.2.1.7, 14.2.1.9, and 14.2.1.12

For all endpoints, a negative change indicated an improvement in the sign or symptom being measured. Statistically significant results favoring KPI-121 0.25% over vehicle were observed for 3 of the 4 primary endpoints defined for this study. For inferior corneal staining scores, the between-group difference in change from baseline at the Day 15 visit was -0.08, favoring KPI-121 0.25% over vehicle, but not reaching statistical significance (p = 0.11).

Efficacy Endpoints - Primary Endpoints KPI-121-C-007

Table 7 - Summary of Primary Efficacy Results KPI-121-C-007

Primary Endpoint (Population)	KPI-121 0.25% (N = 452)		Vehicle (N = 453)		Trt Diff p-value ^a
	Day 1	Change at Day 15	Day 1	Change at Day 15	
Primary ocular sign endpoint					
Conjunctival hyperemia scores ^b at Day 15 visit (ITT, mean [SD])	n = 452 2.0000 (0.62470)	n = 446 -0.3812 (0.60560)	n = 453 2.0397 (0.56694)	n = 447 -0.2371 (0.62256)	-0.16 < 0.0001
Primary ocular symptom endpoint					
ODS scores ^c at Day 15 (ITT; mean [SD])	n = 452 68.79 (15.459)	n = 445 -11.14 (19.901)	n = 453 68.70 (15.799)	n = 444 -9.24 (17.002)	-1.87 0.1298

ITT = intent to treat; ODS = ocular discomfort severity; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle) using least square means

^a P-values were calculated based on an analysis of covariance with baseline value as covariate and treatment group and randomization strata as fixed effects.

^b Conjunctival hyperemia scores (using the CCLRU grading scale, from 0 [none] to 4 [severe]) were based on photographic assessment at a central masked reading center, in the worst region (as defined from evaluations of photographs at Day 1) of the study eye. The study eye was defined using an algorithm described in the statistical analysis plan.

^c ODS scores (from 0 to 100 mm) were derived from data entered into diaries by subjects. Scores were general evaluations across both eyes; there were not separate questions for each eye. Higher scores indicate more severe ocular discomfort. Three-day means were calculated using available data from the 3 days prior to Day 15 (regardless of when Visit 4 [ie, the Day 15 visit] occurred) and the 3 days prior to Day 1. Only available data are used without imputation; if the target number of prior days of diary data was not available, the number of days contributing to the average could be less than the target.

Source: Table 14.2.1.1, 14.2.1.3

Statistically significant results favoring KPI-121 0.25% over vehicle were observed for 1 of the 2 primary endpoints defined for this study. A statistically significant between-group difference was observed for the primary efficacy endpoint of change from baseline in bulbar conjunctival hyperemia scores in the worst region of the study eye (determined based on Day 1 photographs) at the Day 15 visit, based on masked photographic assessment conducted at a central photographic reading center. The between-group difference was -0.16 favoring KPI-121 0.25% over vehicle ($p < 0.01$).

For the primary efficacy endpoint of change in ODS scores from Day 1 to Day 15 using 3-day means, the between-group difference was -1.87 mm, favoring KPI-121 0.25% over vehicle, but not achieving statistical significance ($p = 0.13$).

Summary Efficacy Statement

The applicant has conducted one Phase 2 study (Trial KPI-121-C-002) and two Phase 3 studies (Trial KPI-121-C-006 and -007) to support the efficacy and safety of the drug product for this indication. Each of the 3 studies demonstrated superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary sign endpoint at Day 15. Only Trial KPI-121-C-006 demonstrated superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary symptom endpoints. Trial KPI-121-C-002 and Trial KPI-121-C-007 failed to demonstrate superiority of loteprednol etabonate ophthalmic suspension, 0.25% for their primary symptom endpoint.

In order to support an indication of the temporary relieve of signs and symptoms of dry eye disease, an additional trial is recommended demonstrating statistical superiority of the product over vehicle in the temporary treatment of dry eyes.

9. Safety

From the Clinical review dated 7/30/2019:

The primary evidence of safety reported within this new drug application to support EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is based on integrated data for the safety populations from 3 multicenter, double-masked, randomized, vehicle-controlled dry eye trials (Trials -002, -006, and -007). All 3 trials included KPI-121 0.25% QID and vehicle QID. Trial -002 included a 28-day treatment period, and Trials -006 and -007 included 14-day treatment periods. In all trials, the same formulations of KPI-121 0.25% and vehicle were used.

For Trial -002, the treatment period was 28 days and the median duration of exposure to study treatment was 29 days for both treatment groups. For Trials -006 and -007, the treatment periods were 14 days and the median duration of exposure was 15 days for both treatment groups in both trials.

Serious Adverse Events

Table 5 - Treatment-Emergent Serious Adverse Events (Integrated Safety Population, Trials KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007)

Serious adverse events reported for the studies were consistent with the patient population:

- Subject (b) (6) (002) reported cholelithiasis on Day 29, severe in intensity. It resolved without sequelae within 24 hours of onset and resulted in the subject's discontinuation from the study.
- Subject (b) (6) (007) reported "diverticulum intestinal" on Day 3, which was moderate in severity. It resolved on Day 6 following treatment with a concomitant medication.
- Subject (b) (6) (007) reported hip fracture on Day 4, which was severe. It resolved on Day 15 following surgical repair and resulted in the subject's discontinuation from treatment.

- Subject (b) (6) (007) reported intervertebral disc protrusion on Day 11, which was severe. It resolved on Day 23 following treatment with concomitant medication.

Treatment Emergent Adverse Events

AEs were reported by 15% (143/983) and 13% (123/987) of subjects in the KPI-121 0.25% QID and vehicle QID groups, respectively. The most frequently reported preferred term was instillation site pain, which was reported by 6% of subjects in the KPI-121 0.25% QID group and 6% of subjects in the vehicle QID group. All other AEs were reported by $\leq 1\%$ of subjects in the KPI-121 0.25% QID group.

Table 9 - Number (%) of Subjects Reporting Common ($\geq 1\%$ in Either Treatment Group) Adverse Events (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 983)	Vehicle QID (N = 987)
Number (%) of Subjects Reporting Any AE ^a	143 (14.5)	123 (12.5)
General Disorders and Administration Site Conditions ^a	67 (6.8)	62 (6.3)
Instillation Site Pain	61 (6.2)	56 (5.7)
Eye Disorders ^a	40 (4.1)	50 (5.1)
Eye Irritation	8 (0.8)	12 (1.2)

AE = adverse event; PT = preferred term; QID = four times daily; SOC = system organ class

^a The numbers and percentages for overall AEs and AEs by SOC are inclusive of all PTs. PTs are only included in the table if $\geq 1\%$ of subjects in either treatment group reported that AE.

Note: at each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

Source: Module 5.3.5.3, ISS Table 3.2.1

Summary Safety Statement

The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of EYSUVIS for ten days can be monitored with slit lamp and fundus examinations.

The most frequently reported preferred term was instillation site pain, which was reported by 6% of subjects in the KPI-121 0.25% QID group and 6% of subjects in the vehicle QID group. All other AEs were reported by $\leq 1\%$ of subjects in the KPI-121 0.25% QID group.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

11. Pediatrics

This application was presented at the Pediatric Review Committee on March 13, 2019, with the proposed indication of temporary relief of the signs and symptoms of dry eye disease. This application triggers PREA as a new indication. The applicant requested full waiver for pediatrics birth to less than 17 years of age because studies are impossible or highly impracticable. The PeRC agrees with the request for full waiver as presented in the Agreed iPSP. Formal labeling review and negotiation is deferred until additional data is submitted to support the proposed indication.

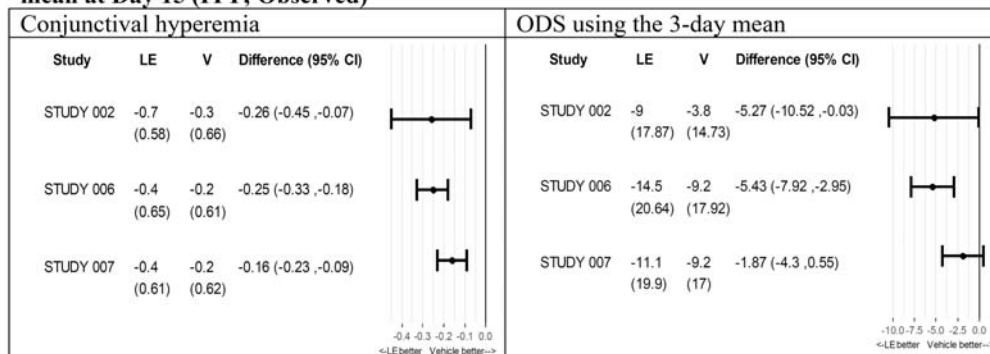
12. Other Relevant Regulatory Issues

BIOSTATISTICS

From the Biostatistics review dated 5/13/2019:

The three studies showed consistent primary sign results. Both Phase 3 studies demonstrated superiority of the LE 0.25% to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15 as shown in Figure 1. The Phase 2 study also demonstrated superiority of the LE 0.25% to the vehicle for its own primary sign endpoint and for the Phase 3 studies' primary sign endpoint.

Figure 1: Change from Baseline in Conjunctival Hyperemia and ODS using the 3-day mean at Day 15 (ITT; Observed)



Source: Summary of Clinical Efficacy, Tables 9 and 14. 95% confidence interval (CIs) are calculated by this reviewer.

Note: ITT = Intent-to-Treat population. In Study 002, ITT population was defined as all randomized subjects with at least 1 post baseline evaluation. In Studies 006 and 007, ITT population was defined as all randomized subjects with at least 1 dose of study treatment. LE = LE 0.25%, V = Vehicle.

The three studies, however, showed less consistent primary symptom results. Only Study 006 demonstrated superiority of the LE 0.25% to the vehicle for the primary symptom endpoints. Studies 002 and 007 failed to demonstrate superiority of LE 0.25% for their primary symptom endpoint, although they both showed numerical favorable results (see Table 7 for completed primary symptom results).

Table 7: Results for the Primary Symptom Endpoints (ITT; Observed)

Study	Endpoint	LE 0.25% QID	Vehicle QID	LE 0.25% QID - vehicle	
		Mean (SD)	Mean (SD)	Difference (95% CI)	P-value
Study 002	Mean ODS at Day 29	n = 73 57.1 (23.90)	n = 77 60.5 (19.77)	-2.64 (-8.51, 3.24)	0.3764
Study 006	CFBL in ODS at Day 15	n = 455 -14.5 (20.64)	n = 452 -9.2 (17.92)	-5.43 (-7.92, -2.95)	<0.001
	CFBL in ODS at Day 15 in subgroup of ODS ≥ 68 mm 1 day prior to Day 1	n = 257 -16.7 (21.94)	n = 264 -10.8 (18.04)	-5.9 (-9.35, -2.44)	<0.001
Study 007	CFBL in ODS at Day 15	n = 445 -11.1 (19.9)	n = 444 -9.2 (17)	-1.87 (-4.3, 0.55)	0.1298

Source: KPI-121-002 CSR, Table 11; KPI-121-006 CSR, Table 11; KPI-121-007 CSR, Table 11; reviewer's analysis in blue
Note: The estimated treatment difference (95% CI and p-value) was based on an ANCOVA model with treatment, baseline values, and stratification variables.

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)

The Division of Medication Error Prevention and Analysis (DMEPA) concluded that proposed proprietary name, Eysuvis, was conditionally acceptable in a letter dated 2/22/2019.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

OPDP was not consulted this review cycle. Formal labeling review and negotiation is deferred until additional data is submitted to support the proposed indication.

FINANCIAL DISCLOSURE: COVERED CLINICAL STUDIES): KPI-121-C-002, -006, AND -007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>140</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>1</u> Significant equity interest held by investigator <u>0</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>140</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)



OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

The Office of Scientific Investigations (OSI) completed a review dated 6/14/2019. The clinical sites of Drs. Whitsett, Rauchman, and Nichols were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007) appear to have been conducted adequately. The final compliance classifications of the inspections of Drs. Whitsett, Rauchman, and Nichols were No Action Indicated (NAI).

Site # Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site #124 Jeffery Whitsett, M.D. Whitsett Vision Group 1237 Campbell Road Houston, TX 77055	KPI-121-C-002 Subjects: 35	22 Jan–12 Mar 2019	NAI
Site #130 Steven H. Rauchman, M.D. North Valley Eye Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	KPI-121-C-006 Subjects: 95	4-8 Feb 2019	NAI
Site #133 Kelly Kinney Nichols, O.D., Ph.D. University of Alabama at Birmingham School of Optometry Henry Peters Building 1716 University Blvd. Birmingham, AL 35294	KPI-121-C-007 Subjects: 114	25-27 Feb 2019	NAI

Key to Compliance Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations. Data unreliable.

13. Postmarketing Recommendations

There are no postmarket risk evaluations or mitigation strategies recommended except the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product.

14. Labeling

Formal labeling review and negotiation is deferred until additional data is submitted to support the proposed indication.

15. Recommended Comments to the Applicant

The following comments will be conveyed to the applicant in the Complete Response regulatory action letter:

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically:

- a. Phase 2 study (Trial KPI-121-C-002) failed to demonstrate superiority of loteprednol etabonate ophthalmic suspension, 0.25% for its primary symptom endpoint, although it showed numerically favorable results.
- b. Phase 3 study (Trial KPI-121-C-007) failed to demonstrate superiority of loteprednol etabonate ophthalmic suspension, 0.25% for its primary symptom endpoint, although it showed numerically favorable results.

It is recommended that an additional clinical trial be conducted demonstrating replication of the sign and symptom results from KPI-121-C-006 to provide substantial evidence of efficacy of the drug product in the intended patient population.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
08/07/2019 06:34:26 AM

WILEY A CHAMBERS
08/07/2019 08:13:46 AM

Clinical Review
William M. Boyd, M.D.
NDA 210933 Original
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

CLINICAL REVIEW of NDA 210933

Application Type	NDA
Application Number(s)	210933
Priority or Standard	Standard
Submit Date(s)	10/15/2018
Received Date(s)	10/15/2018
PDUFA Goal Date	8/15/2019
Division/Office	OND
Reviewer Name(s)	William M. Boyd, M.D.
Review Completion Date	7/15/2019
Established/Proper Name	loteprednol etabonate ophthalmic suspension, 0.25%
(Proposed) Trade Name	EYSUVIS
Applicant	Kala Pharmaceuticals, Inc.
Dosage Form(s)	ophthalmic suspension
Proposed Dosing Regimen(s)	Instill one to two drops into each eye four times daily for two weeks
Proposed Indication	temporary relief of the signs and symptoms of dry eye disease
Recommendation on Regulatory Action	Recommend Complete Response

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement

Clinical Review

William M. Boyd, M.D.

NDA 210933 Original

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
TEAE	treatment emergent adverse event

1. 1. Executive Summary

1.1. Product Introduction

This is a 505(b)(2) new drug application for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%. The reference listed drug is LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, NDA 020583. The Applicant's bridge consists of chemical identity, comparative nonclinical pharmacokinetics (PK), and comparative clinical PK. In this review, EYSUVIS may also be referred to as KPI-121 0.25%.

Loteprednol etabonate is a corticosteroid. Corticosteroids have been shown to inhibit the inflammatory response to a variety of inciting agents. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms.

Ocular AEs generally associated with ophthalmic steroids include elevated intraocular pressure (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis. Topical ophthalmic corticosteroid products are approved for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitis when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation; corneal injury from chemical, radiation, or thermal burns, or penetration of foreign bodies. Kala believes a significant unmet need exists for a safe and effective corticosteroid product to provide reliable temporary relief of the signs and symptoms of dry eye. The applicant has proposed a two-week dosing to potentially address the known ocular adverse event profile of corticosteroids. Topical ophthalmic corticosteroid products have typically included a Warning about the need for additional monitoring, if the product is used for more than 10 days.

1.2. **Conclusions on the Substantial Evidence of Effectiveness**

BLA 210933, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, is not recommended for approval. The clinical trials submitted in this application do not support an indication for the temporary relief from the signs and symptoms of dry eye disease. In order to support an indication of the signs and symptoms of dry eye disease, at least one additional trial is recommended demonstrating replication of the sign and symptom results from KPI-121-C-006.

1.3. **Benefit-Risk Assessment**

Studies -002, --006 and -007 demonstrated superiority of EYSUVIUS to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15. However, only -006 demonstrated superiority of EYSUVIS to the vehicle for the primary symptom endpoint; -002 and -007 failed to demonstrate superiority. While study -002 may have been underpowered to demonstrate a difference in a symptom, an additional trial should be conducted prior to accepting the results from KPI-121-C-006. The clinical trials contained in this application demonstrated that the potential adverse events associated with the use of EYSUVIS for ten days can be monitored with slit lamp and fundus examinations.

Clinical Review
William M. Boyd, M.D.
NDA 210933 Original
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The health and function of the cornea is dependent on a thin tear film layer made up of an aqueous, mucin, lipids, lysozymes, immunoglobulins, glucose, and salts. In keratoconjunctivitis sicca (dry eye), one or more of the components is deficient.	Keratoconjunctivitis sicca (dry eye) is a potentially debilitating condition which can impede the activities of daily living and can be associated with anterior segment damage to the eye.
Current Treatment Options	Currently available treatments for keratoconjunctivitis sicca (dry eye) include the use of OTC demulcents, Rx topical calcineurin inhibitors (cyclosporine ophthalmic emulsion and cyclosporine ophthalmic solution), and/or a lymphocyte function-associated antigen-1 (LFA-1) antagonist.	This product, if approved, would provide an alternative product to temporarily treat the signs and symptoms of dry eye disease.
Benefit	Three studies demonstrated superiority of EYSUVIS to the vehicle for the primary sign endpoint of change from baseline in conjunctival hyperemia at Day 15, however, only one of these studies demonstrated superiority of EYSUVIS to the vehicle for the primary symptom endpoint.	An additional trial is recommended to support the sign and symptom results from KPI-121-C-006.
Risk and Risk Management	Serious adverse reactions associated with ophthalmic corticosteroids include elevated IOP, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.	The potential serious adverse events associated with the use of topical ophthalmic corticosteroids can be managed with limitations on dosing for ten days and monitoring with slit lamp examinations.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Section 6.1.1, 6.2.1 and 6.3.1 and Sections 6.1.2, 6.2.2, and 6.3.2
☒	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerFO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Keratoconjunctivitis sicca (KCS), commonly referred to as dry eye, is a disease affecting the ocular surface, the tear film, and related ocular tissues and organs. The ocular surface is supported and maintained by the tear film, which is composed of 3 distinct components (lipid, aqueous, and mucin) that make up 2 fluid layers. Meibomian glands along the upper and lower lid margins produce the outer lipid layer of the tear film. The inner layer, an aqueous and mucin mixture, is composed of aqueous fluid produced by the main and accessory lacrimal glands and mucins produced by goblet cells on the conjunctival epithelium as well as corneal epithelial cells.

Signs of dry eye include, but are not limited to, corneal staining, conjunctival staining, decreased tear breakup time, decreased Schirmer's tear test with or without anesthesia. Symptoms of dry eye include, but are not limited to, blurred vision, light sensitivity, sandy/gritty feeling, ocular irritation, ocular pain or discomfort, ocular itching.

Safety and efficacy for the treatment of dry eye disease indication is recommended to be demonstrated in adequate and well-controlled, independent trials. A demonstration of a statistically significant difference between the test treatment and vehicle for at least one objective sign and at least one subjective symptom of dry eye is expected. Increases of ≥ 10 mm in Schirmer wetting from baseline have been validated (i.e. qualified) as being clinically relevant based on correlation with decreased corneal staining.

2.2. Analysis of Current Treatment Options

Table 1 - FDA Approved Treatments

Indication:	To increase tear production	
Restasis	cyclosporine ophthalmic emulsion	NDA 50-790
Cequa	cyclosporine ophthalmic solution	NDA 210913
Indication:	To treat signs and symptoms of dry eye disease	
Xiidra	lifitegrast ophthalmic solution	NDA 208073

Current management of dry eye disease often begins with artificial tear replacement and other palliative treatments such as punctal occlusion.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Loteprednol etabonate (LE) is a corticosteroid that was originally developed as a topical ophthalmic suspension 0.5% [LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, NDA 020583]. LOTEMAX is approved for the treatment of steroid responsive inflammatory conditions when the inherent hazard of steroid use is accepted to obtain an advisable diminution of edema and inflammation and for the treatment of postoperative inflammation following ocular surgery.

3.2. Summary of Presubmission/Submission Regulatory Activity

A Pre-IND (IND 17192) meeting was held between the sponsor and the FDA on April 4, 2013.

A Type C, End of Phase 2 meeting was held on May 3, 2016.

A CMC pre-NDA meeting was held on May 12, 2017.

A Type B Pre-NDA meeting was held on August 16, 2017. The purpose of the meeting was to discuss the statistical analysis plan for the ongoing Phase 3 trials and format and content of the nonclinical and clinical modules of the upcoming NOA submission.

A Type C Guidance meeting was held on May 8, 2018, to discuss the results of their Phase 2 and Phase 3 clinical trials for KPI-121 0.25% and whether their product has sufficient safety and efficacy data for an NDA application with an indication of temporary relief of the signs and symptoms of dry eye disease. Based on the summary clinical data provided in the meeting package, it did not appear that the applicant had adequate and well-controlled trials to support the approval of an NDA. While STRIDE 1 (Study KPI-121-C-006) appeared to meet its coprimary sign and symptom endpoints, the results were not replicated in STRIDE 2 (Study KPI121-C-007). Study KPI-121-C-002, the Phase 2 trial, also failed to meet its co-primary sign and symptom endpoints.

3.3. Foreign Regulatory Actions and Marketing History

At the time of this submission, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% has not been marketed in any region globally.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

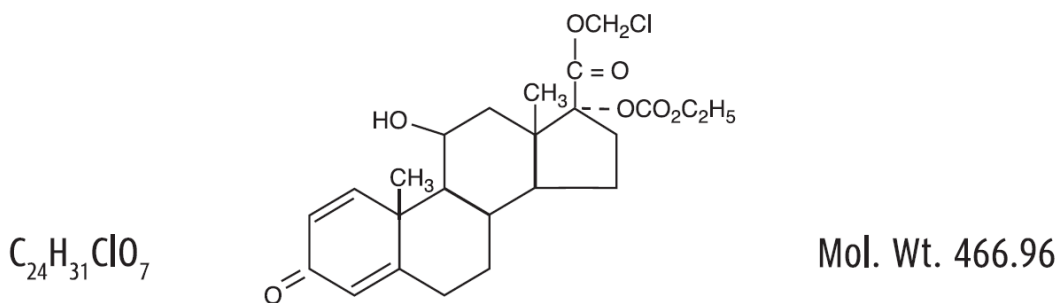
4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) completed a review dated 6/14/2019. The clinical sites of Drs. Whitsett, Rauchman, and Nichols were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007) appear to have been conducted adequately. The final compliance classifications of the inspections of Drs. Whitsett, Rauchman, and Nichols were No Action Indicated (NAI).

See the CDTL memorandum for more detail.

4.2. Product Quality

EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is a sterile aqueous suspension of loteprednol etabonate (LE) for topical ophthalmic use. Each milliliter contains 2.5 mg LE as the active ingredient. Loteprednol etabonate is represented by the following structural formula:



The quantitative composition and function of each component in EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is listed in the following table.

(b) (4)

Clinical Review
William M. Boyd, M.D.
NDA 210933 Original
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Table 2 - Composition of EYSUVIS 0.25%

Ingredient	Quality Standard	Function	Amount (mg) in each mL of EYSUVIS 0.25%	Concentration (%w/v) in EYSUVIS 0.25%
Loteprednol etabonate	(b) (4)	Active Pharmaceutical Ingredient	2.5	0.25
Glycerin	USP-NF	(b) (4)		
Sodium citrate, dihydrate	USP-NF			
Sodium chloride	USP-NF			
Poloxamer 407	USP-NF			
Edetate disodium, dihydrate	USP-NF			
Citric acid, (b) (4)	USP-NF	(b) (4)		
Benzalkonium chloride	USP-NF			
Water for injection	USP-NF			
(b) (4)				
(b) (4)				
USP-NF: United States Pharmacopeia - National Formulary				
(b) (4)				

Source: Module 2.3.P

Table 3 - Quality control specifications for release of EYSUVIS 0.25% commercial fill bottles

Attribute and Test	Method Number	Acceptance Criteria
Appearance	(b) (4) Visual Observation	White dropper bottle (b) (4)
pH	(b) (4)	
Osmolality		
Benzalkonium Chloride Assay		
Particle Size		
Minimum Fill Volume	USP<755>	(b) (4)
Identity Loteprednol Etabonate (LE)	(b) (4)	
Assay Loteprednol Etabonate		

Attribute and Test	Method Number	Acceptance Criteria
Loteprednol Etabonate related impurities ¹ A. Loteprednol Etabonate related substances and impurities B. Total of all related impurities	(b) (4)	
EDTA Assay		
Sterility	USP<71>	Meets USP test requirements

NMT = Not More Than;
dihydrate

(b) (4)

EDTA = edetate disodium,

(b) (4)

Source: Module 2.3.P

The container closure system for EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% consists of a white low-density polyethylene (LDPE) plastic bottle with nominal capacity of 10 mL; a controlled-drop, linear LDPE (LLDPE) tip; and a pink high-density polyethylene (HDPE) 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.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

Loteprednol etabonate (LE) is a corticosteroid ester initially approved in 1998 (Bausch & Lomb's NDA 20-583 for LOTEMAX). From a nonclinical perspective, the NDA relies on Kala's own studies, and FDA's finding of safety for the approved listed drug LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, approved under NDA 20-583. The nonclinical Pharmacology/Toxicology (P/T) review identified no new safety concerns for EYSUVIS.

4.5. Clinical Pharmacology

Study KPI-121-C-009 characterized the PK exposure of LE in 20 healthy adult subjects. Plasma concentrations of LE, and the inactive metabolites, PJ-90 and PJ-91, were analyzed using a validated LC/MS/MS method. The analytical ranges of the assay were validated from 1.00 to 1,000 ng/mL for LE and PJ-91 and the lower limit of assay quantitation (LLOQ) was 1.00 ng/mL. The analytical ranges of the assay were validated from 5.00 to 5,000 ng/mL for PJ-90 and the LLOQ was 5.00 ng/mL.

All plasma concentrations of LE, PJ-90, and PJ-91 at every time point pre-and post-instillation of 2 drops of EYSUVIS 0.25% in each eye QID for 15 days were BLQ (Below the Limit of Quantitation). Thus, the Applicant was unable to characterize the PK parameters for LE, PJ- 90, and PJ-91.

4.6. Devices and Companion Diagnostic Issues

There are no device or companion diagnostic issues for this application.

4.7. Consumer Study Reviews

There are no consumer study reviews for this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Clinical Review
William M. Boyd, M.D.
NDA 210933 Original
EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Table 4 - Table of Clinical Studies

Protocol Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects ^a	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Trial Status; Type of Report
<i>Module 5.3.3.1 – Healthy Subject PK and Initial Tolerability Study Reports</i>							
KPI-121-C-009	Systemic PK of LE and its major metabolites, PJ-90 and PJ-91	Phase 1, single center, open-label, PK study of KPI-121, no control group	KPI-121 0.25% QID 2 drops OU	20 total	Healthy adults	15 days	Completed Full
<i>Module 5.3.5.1 – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication</i>							
KPI-121-C-002	Efficacy and safety of KPI-121 compared to vehicle	Phase 2, multi-center, randomized, double-masked, parallel- group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	150 total: 73 KPI-121 0.25% 77 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	28 days of treatment preceded by a 14-day vehicle run- in period	Completed Full
KPI-121-C-006 (STRIDE 1)	Efficacy and safety of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel- group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	915 total: 459 KPI-121 0.25% 456 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	14 days of treatment preceded by a 14-day vehicle run- in period	Completed Full
KPI-121-C-007 (STRIDE 2)	Efficacy and safety of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel- group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	905 total: 452 KPI-121 0.25% 453 Vehicle	Male and female subjects age ≥18 years with a clinical diagnosis of DED	14 days of treatment preceded by a 14-day vehicle run- in period	Completed Full

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Protocol Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects ^a	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Trial Status; Type of Report
<i>Module 5.3.5.4 – Other Study Reports</i>							
KPI-121-C-001	Efficacy and safety of 2 concentrations of KPI-121 compared to vehicle	Phase 3, multi-center, randomized, double-masked, parallel- group study of 2 concentrations and dosing regimens of KPI-121 vs. vehicle	KPI-121 0.25% QID KPI-121 1% BID Vehicle A QID Vehicle B BID 1 to 2 drops in the study eye	380 total: 125 KPI 121 1% 129 KPI-121 0.25% 126 Vehicle ^b	Male and female subjects age ≥18 years who had undergone routine cataract surgery	14 days	Completed Full
KPI-121-C-003	Efficacy and safety of KPI-121 compared to vehicle	Phase 2, multi-center, randomized, double-masked, parallel- group study of KPI-121 vs. vehicle	KPI-121 0.25% QID Vehicle QID 1 to 2 drops OU	205 total: 104 KPI-121 0.25% 101 Vehicle	Male and female subjects age ≥18 years with signs and symptoms of inflammatory MGD	28 days of treatment preceded by a 14-day vehicle run-in period	Completed Abbreviated
KPI-121-C-004	Exploratory safety and efficacy of 2 concentrations of KPI-121	Exploratory, multi-center, randomized, single-masked, parallel-group study of 2 concentrations of KPI-121	KPI-121 1% QID KPI-121 0.25% QID 1 to 2 drops in the study eye	15 total: 9 KPI-121 0.25% 6 KPI-121 1%	Male and female subjects age ≥ 18 years with documented presence of intraretinal or subretinal fluid secondary to RVO or DME	28 days	Completed Synoptic

BID = twice daily; DED = dry eye disease; DME = diabetic macular edema; KPI = Kala Pharmaceuticals, Incorporated; LE = loteprednol etabonate; MGD = meibomian gland disease; OU = both eyes; PK = pharmacokinetic; QID = four times daily; RVO = retinal vein occlusion

^a Number of subjects is presented for the safety population, which is defined as all randomized subjects receiving study treatment and having at least one postbaseline safety assessment.

^b Number of subjects in the Vehicle group in Study KPI-121-C-001 was the total for Vehicle groups A and B, which were pooled for all analyses.

5.2. Review Strategy

The primary evidence of efficacy reported within this new drug application to support EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% for the temporary relief of the signs and symptoms of dry eye disease is based on data from 3 multicenter, double-masked, randomized, vehicle-controlled dry eye trials (Trials KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007). All 3 dry eye trials included 2 treatment groups: KPI-121 0.25% QID and vehicle QID. Trial KPI-121-C-002 included a 28-day treatment period, and Trials KPI-121-C-006 and KPI-121-C-007 included 14-day treatment periods. In all 3 trials, a run-in period preceded the treatment period wherein all subjects applied KPI-121 vehicle QID for 2 weeks.

In all trials, the same formulations of KPI-121 0.25% and vehicle were used.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial KPI-121-C-002

A Phase 2, Double-Masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease

6.1.1. Study Design

Trial Design

This was a Phase 2, multicenter, double-masked, randomized, vehicle-controlled, parallel-group study designed to evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension dosed four times per day (QID) in treating the signs and symptoms of dry eye disease. Subjects with dry eye disease who met all other eligibility criteria at Visit 1 (Screening) entered a 14-day (± 1 day) run-in period of QID dosing in each eye with single-masked vehicle. At Visit 2 (Day 1/Randomization), subjects who continued to meet eligibility criteria were randomized in an approximate 1:1 ratio to either KPI-121 0.25% ophthalmic suspension or vehicle for the double masked treatment period. Randomization was stratified based on subjects' Modified (Symptom Assessment in Dry Eye) SANDE Severity Scores (>50 mm to 70 mm, >70 mm to 100 mm) on the day prior to Day 1 and the Investigator-rated bulbar conjunctival hyperemia scores (2, ≥ 3) in the designated study eye on Day 1. Study treatment was self-administered as 1 to 2 drops in each eye QID for 28 days.

Table 5 - Summary of Procedures KPI-121-C-002

Procedures	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	Random-ization	Diary Collection	Study Visit	Diary Collection	End of Study
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Day 29 (±1 day)
Informed Consent, HIPAA Authorization, Medical History	X					
Concomitant medication query	X	X	X	X	X	X
Urine pregnancy test ^a	X					X
Inclusion/Exclusion	X	X				
Adverse Events Assessment	X	X	X	X	X	X
Subject-rated assessment of ocular discomfort	X	X	X	X	X	X
Modified SANDE Assessment (subject diary)	X	X ^b	X ^b	X ^b	X ^b	X ^b
Investigator-rated assessment of bulbar conjunctival hyperemia	X	X		X		X
Bulbar conjunctival hyperemia photography		X		X		X
Best-corrected visual acuity	X	X		X		X
Slit lamp biomicroscopy	X	X		X		X
Corneal fluorescein staining	X	X		X		X
Lissamine green conjunctival staining	X	X		X		X
Unanesthetized Schirmer Test Assessment	X					
Intraocular pressure measurement	X	X		X		X
Dilated ophthalmoscopy	X					X
Study treatment administration in-clinic	X ^c	X				
Dispense investigational product	X ^c	X		X		
Dispense subject diary	X	X	X	X	X	
Collect investigational product		X ^c				X
Collect subject diary		X	X	X	X	X

SANDE = Symptom Assessment in Dry Eye

^a Women of childbearing potential only

^b Collected through use of subject diary

^c Run-in product

Study Endpoints KPI-121-C-002

The set of primary endpoints, using hierarchical statistical testing, was:

1. Comparison of mean bulbar conjunctival hyperemia scores based on photographic assessment of the worst region (nasal, temporal, or central; as determined at baseline) of the study eye between the KPI-121 0.25% and vehicle groups at Day 29 (or final visit)
2. Comparison of mean Modified SANDE Severity Scores between the KPI-121 0.25% and vehicle groups using the mean of scores over the 7 days prior to the Day 29 visit (or final visit).

Photographic assessments of hyperemia were conducted using a masked photographic reading center.

Principle Inclusion/Exclusion Criteria KPI-121-C-002

Inclusion: At Screening and Day 1/Randomization, individuals of either gender or any race were eligible for study participation if they:

1. Were 18 years of age or older

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2. Had a documented clinical diagnosis of dry eye disease in both eyes
3. Had ongoing dry eye disease as defined by the following criteria in the same eye or both eyes:
 - a. A corneal fluorescein staining score at Screening and Day 1 of ≥ 6 NEI (National Eye Institute) scale AND
 - b. Bulbar conjunctival hyperemia at Screening and Day 1 of ≥ 2 as assessed using the Cornea and Contact Lens Research Unit (CCLRU) scale AND
 - c. A score of > 50 mm on Modified SANDE Severity at Screening AND a score of > 40 mm on Modified SANDE Severity on the day prior to Day 1 AND
 - d. An unanesthetized Schirmer Test score at Screening of ≤ 10 mm
4. Were women of child-bearing potential who were not pregnant or lactating and not sexually active (i.e., abstinent), or women of child-bearing potential who were not abstinent must have been using an acceptable methods of birth control

Exclusion: In order for subjects to be eligible at Screening and Day 1/Randomization, they may not:

1. Have had a known hypersensitivity or contraindication to the investigational product(s) or their components.
2. Have used any of the following medications within 30 days prior to Screening or for the duration of the study:
 - a. ocular, inhaled, or intranasal corticosteroids
 - b. ocular or oral non-steroidal anti-inflammatory drugs (NSAIDs) with the exception of ≤ 81 mg/day of acetylsalicylic acid (ASA or aspirin)
 - c. topical ocular antibiotics
 - d. topical ocular antihistamines or mast cell stabilizers
 - e. oral antihistamines
 - f. topical or nasal vasoconstrictors
3. Have used any of the following medications within 60 days prior to Screening or for the duration of the study:
 - a. topical cyclosporine (Restasis)
 - b. any form of topical LE
4. Have altered oral dosing of the following within 30 days prior to Screening or anticipated alteration of dosing during the study.
 - a. tetracycline compounds (eg, tetracycline, doxycycline, or minocycline)
 - b. omega-3 or omega-6 supplements
5. Have altered dosing of the following medications within 6 months prior to Screening or anticipated alteration of dosing during the study:
 - a. anticholinergics
 - b. antidepressants
 - c. isotretinoin
 - d. oral corticosteroids
 - e. systemic immunosuppressive agents

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6. Have been unwilling to abstain from the use of any topical ophthalmic medications at Screening and for the duration of the study, including:

- a. eyelash growth medications
- b. eye drops, gels, or artificial tears

7. Have been unwilling to abstain from the use of tumor necrosis factor (TNF)-blocking agents (e.g., etanercept, adalimumab, infliximab) at Screening and for the duration of the study

8. Have been currently receiving treatment for glaucoma at Screening or for the duration of the study and/or had history of or current glaucoma, or an intraocular pressure (IOP) over 21mmHg at Screening or Day 1/Randomization.

9. Have been unwilling to abstain from wearing contact lenses for 14 days prior to Screening and for the duration of the study

10. Have been monocular or had a best-corrected visual acuity (BCVA), using corrective lenses if necessary, of +1.0 logMAR or worse as assessed by ETDRS (Early-Treatment Diabetic Retinopathy Study)

11. Have had penetrating intraocular surgery within 3 months prior to Screening or anticipated requiring penetrating intraocular surgery during the study

12. Have had eyelid surgery within 6 months prior to Screening or anticipated requiring eyelid surgery during the study

13. Have had congenitally absent lacrimal glands or meibomian glands

14. Have had Selective Laser Trabeculoplasty (SLT) within 3 months prior to Screening or anticipated requiring SLT

15. Have had cauterization of the punctum or had punctal plugs (silicone or collagen) inserted or removed less than 3 months prior to Screening or planned during the study.

NOTE: If subject started the study with punctal plugs, they were to remain in place for the duration of the study and be replaced if inadvertently removed.

16. Have had corneal refractive surgery, glaucoma surgery, or corneal transplantation (full thickness, anterior or posterior) within 1 year prior to Screening

NOTE: This exclusion also applies if surgery was performed greater than 1 year prior to Screening but the Investigator considered the subject to be unstable and/or require medication.

17. Have had a diagnosis of:

- a. ongoing ocular infection
- b. moderate to severe pinguecula or pterygia
- c. Stevens-Johnson Syndrome
- d. significant conjunctival scarring
- e. significant anterior blepharitis
- f. severe/serious ocular condition that in the judgment of the investigator could have confounded study assessments or limited compliance
- g. severe/serious systemic disease or uncontrolled medical condition that in the judgment of the investigator could have confounded study assessments or limited

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compliance

18. Have had corneal fluorescein staining with diffuse confluent staining more than 33% of area (focal confluent staining was acceptable), over 5 filaments or epithelial defects

19. Have had active or had an outbreak of herpetic keratitis within 1 year of Screening

20. Have had meibomian gland disease at Screening or Day 1/Randomization as defined by displaying ALL 3 of the following in the same or both eyes:

a. a clinical sign severity score of 2 (moderate) or greater on posterior lid margin hyperemia

b. a clinical sign severity score of 2 (moderate) or greater on the character of the meibomian glands' contents

c. a clinical sign severity score of 2 (moderate) or greater on the expressibility of the meibomian glands

Investigational Products KPI-121-C-002

KPI-121 0.25% ophthalmic suspension contained 0.25% (w/v) LE (b) (4) and was supplied in a white, low-density polyethylene plastic dropper bottle with a white, controlled drop, polyethylene tip and a polypropylene cap.

The vehicle control had the same composition as KPI-121 0.25% ophthalmic suspension except that it did not contain LE and was also supplied in the same white, low-density polyethylene plastic dropper bottle with the same white, controlled-drop, polyethylene tip and polypropylene closure as KPI-121 0.25% ophthalmic suspension.

Composition of KPI-121 Study Product KPI-121-C-002

Ingredient	Function	Concentration (% w/v)
Loteprednol etabonate	Active pharmaceutical ingredient	0.25
Poloxamer 407 USP	(b) (4)	(b) (4)
Glycerin USP		
Sodium chloride USP		
(b) (4)		
Disodium edetate, dihydrate USP	Preservative	0.01
Citric acid, (b) (4) USP		
Benzalkonium chloride USP		
(b) (4) water USP		

(b) (4) USP = United States Pharmacopeia; w/v = weight/volume

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Composition of Vehicle KPI-121-C-002

Ingredient	Function	Concentration (% w/v)
Poloxamer 407 USP		(b) (4)
Glycerin USP		
Sodium chloride USP		
(b) (4)		
Disodium edetate, dihydrate USP		
Citric acid, (b) (4) USP		
Benzalkonium chloride USP	Preservative	0.01
(b) (4) water USP		(b) (4)
(b) (4) USP = United States Pharmacopeia; w/v = weight/volume		

Statistical Analysis Plan KPI-121-C-002

Efficacy analyses were performed for all randomized subjects (the intent-to-treat [ITT] population) with at least 1 post-baseline (Baseline = Day 1 visit) assessment. Subjects were analyzed as randomized according to the planned treatment.

The primary efficacy endpoints were evaluated using hierarchical statistical testing. The endpoints were tested at alpha = 0.05 in the pre-specified order listed above.

Bulbar conjunctival hyperemia was assessed by a central masked reader who scored the photographs taken by the site. Photographic procedures are described in the Photography Manual. The Modified SANDE Severity Scores were based on the scale noted in the protocol (Appendix 16.1.1). For hyperemia and staining evaluations, the analyses were based on the designated study eye. SANDE scores were general assessments across both eyes, so study eye designation was not considered.

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Investigators KPI-121-C-002

Site No.	Investigator Name	Sub-Investigator(s) Name	Hospital/Institution Name and Address	Enrolled (Randomized)
111	Joseph Martel, MD	James Martel, MD, MPH Anna Chepurny Diana Chepurny Inna Topal Svetlana Brazhnikova Snow Hu Anton Grach Delores Figueroa Veniamin Melnychuk	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670	43(18)
118	Kenneth Sall, MD	Leticia Guzman Cisneros, CCRC Cindy Lee, CCRC Ilanie Shiell, CCRC Patricia Manjarrez, CCRC	Sall Research Medical Center 11423 187th Street, Suite 200, Artesia, CA, 90701	51(17)
124	Jeffery Whitsett, MD	David Fu, OD Jesse McKey, MD Shiran Narrow Debbie Chmielewski Nitza Tavitav Jenna Wilkins	Whitsett Vision Group 1237 Campbell Road Houston, TX 77055	35(26)
126	Gregg J. Berdy, MD	Ranjan P. Malhotra, MD Robert C. Brusatti, OD Andrew Royer, OD Deborah Gravemann, RN, CCRP Jill Montgomery	Ophthalmology Associates 12990 Manchester Road St. Louis, MO 63131	19(5)
127	David Evans, OD	Eugene McLaurin, MD Don Gayso, OD Daniel J. Ashe Kim Smith Joshua Tyler Arel Kalafat Nelson Carney	Total Eye Care, PA 6060 Primacy Parkway Memphis, TN 38119	43(25)
128	Kathleen Kelley, OD	Matthew Feng, MD Tiffany Schendel Faye Peters, OD Megan McDonald Clorissa Quillin	Price Vision Group 9002 North Meridian Street, Suite #100 Indianapolis, IN 46260	27(26)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Hospital/Institution Name and Address	Enrolled (Randomized)
130	Steven Rauchman, MD	Robert Smyth-Medina, MD Joanne Perry Rocio Rodriguez Rosio Mendoza	North Valley Eye Medical Group 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	38(21)
131	Michael Korenfeld, MD	Nathan M. Tuttle, OD Ashley D. Schmitz, RN Janet Renee Zeitzmann, RN Michelle M. Mueller	Comprehensive Eye Care, Ltd. 901 East 3 rd Street Washington, MO 63090	11(4)
132	Jodi Ian Luchs, MD	Jason Todd Flicker, MD Howard Adam Lane, MD Loraine Huemmer, COT, CRC Debora Losito, COA, CRC Mary Modica, CRC	South Shore Eye Center, LLP 2185 Wantagh Avenue Wantagh, NY 11793	4(0)
137	Marc Abrams, MD	N/A	Abrams Eye Center 2322 E. 22 nd Street, Suite 102 Cleveland, OH 44115	12(8)

6.1.2. Study Results KPI-121-C-002

Compliance with Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Patient Disposition KPI-121-C-002

A total of 283 subjects were screened for the study; 133 were screen failures and 150 were randomized and received study treatment. Of those who were randomized into the study, 148 subjects completed the study. Two subjects discontinued participation during the study; 1 subject in the KPI-121 0.25% group discontinued due to an AE (cholelithiasis) and 1 subject in the vehicle group discontinued for “other” reasons (protocol deviation, use of concomitant medication [Celebrex]).

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	KPI-121 0.25% (N = 73)	Vehicle (N = 77)	Total (N = 150)
Completed Study	72 (98.6%)	76 (98.7%)	148 (98.7%)
Subjects Withdrawn Early from the Study	1 (1.4%)	1 (1.3%)	2 (1.3%)
Reason for Study Exit			
Withdrawal by subject	0	0	0
Adverse event	1 (1.4%)	0	1 (0.7%)
Pregnancy	0	0	0
Physician decision	0	0	0
Lost to follow-up	0	0	0
Other	0	1 (1.3%)	1 (0.7%)

Source: Table 14.1.2.1

Protocol Violations/Deviations KPI-121-C-002

Deviation Category	KPI-121 0.25% (N = 73)	Vehicle (N = 77)
Concomitant Medication Deviation During Masked Period	2	0
Inclusion & Exclusion Criteria ^a	2	1
Missed Procedures	3	1
Other	2	5
Study Product Deviation	12	11
Study Visit Schedule Deviations	6	10

^a Subject (b) (6) (KPI-121 0.25% group) is included in Listing 16.2.2 as a protocol deviation in the category of Inclusion & Exclusion Criteria because the Investigator did not keep the Schirmer strips for the monitor to verify enrollment eligibility (due to the subject's diagnosis of Hepatitis B). However, the subject was deemed eligible to enroll and is not counted in Table 14.1.5 or Listing 16.2.4.2 as an inclusion or exclusion failure.

Source: Listing 16.2.2

Table 6 - Demographic Characteristics KPI-121-C-002

	KPI-121 0.25% (N = 73)	Vehicle (N = 77)	Total (N = 150)
Age (years)			
Mean	56.3	54.9	55.6
SD	17.17	12.29	14.83
Median	58.0	57.0	58.0
Min, Max	18, 88	22, 79	18, 88
Gender, n (%)			
Male	20 (27.4)	16 (20.8)	36 (24.0)
Female	53 (72.6)	61 (79.2)	114 (76.0)
Ethnicity, n (%)			
Hispanic/Latino	15 (20.5)	16 (20.8)	31 (20.7)
Not Hispanic/Latino	58 (79.5)	61 (79.2)	119 (79.3)
Race, n (%)			
American Indian/Alaskan Native	0	0	0
Asian	3 (4.1)	4 (5.2)	7 (4.7)
Black/African-American	10 (13.7)	8 (10.4)	18 (12.0)
Native Hawaiian/Other Pacific Islander	2 (2.7)	1 (1.3)	3 (2.0)
White	54 (74.0)	63 (81.8)	117 (78.0)
Unknown	0	0	0
Other Race	4 (5.5)	0	4 (2.7)
Mixed	0	1 (1.3)	1 (0.7)

ITT = intent to treat; Max = maximum; Min = minimum; SD = standard deviation

Source: Table 14.1.4

The 150 subjects in the ITT and safety datasets were predominantly white females, with a mean (range) age of 55.6 (18 to 88) years (Table 9). No meaningful differences were observed between the treatment groups in terms of demographic characteristics.

Efficacy Results – Primary Endpoints KPI-121-C-002

Table 7 - Summary of Mean Bulbar Conjunctival Hyperemia Scores of the Worst Region as Determined by Photographic Assessment in the Study Eye (ITT Population) KPI-121-C-002

	KPI-121 0.25% (N = 73)	Vehicle (N = 77)	Between-group Difference p-value ^a
Day 1 (Baseline)			
n	73	77	
Mean (SD)	2.18 (0.452)	2.05 (0.426)	
Median	2.00	2.00	
Day 15 (Observed) ^b			
N	73	77	
Mean (SD)	1.52 (0.580)	1.71 (0.686)	-0.26 0.0090 ^c
Median	2.00	2.00	
Min, Max	0, 3	0, 3	
Day 15 (Change From Baseline) ^b			
N	73	77	
Mean (SD)	-0.66 (0.583)	-0.34 (0.661)	-0.26 0.0090 ^d
Median	-1.00	0.00	
Min, Max	-2, 0	-2, 1	
Day 29 (Observed)			
N	72	77	
Mean (SD)	1.44 (0.669)	1.61 (0.588)	-0.21 0.0387 ^c
Median	1.00	2.00	
Min, Max	0, 3	0, 3	
Day 29 (Change From Baseline)			
N	72	77	
Mean (SD)	-0.74 (0.692)	-0.44 (0.639)	-0.21 0.0387 ^d
Median	-1.00	0.00	
Min, Max	-2, 1	-2, 1	

Note: Worst region (nasal, temporal, or central) was defined based on baseline evaluations. Day 29 is the primary timepoint.

^a P-values are 2-sided; significance level is 0.05. Between-group differences are for KPI-121 minus vehicle, where negative values favor KPI-121.

^b Day 15 was evaluated as a secondary endpoint (see [Section 11.2.1](#)), but is presented alongside the results for the primary endpoint (Day 29) to provide a complete summary of mean bulbar conjunctival hyperemia scores of the worst region as determined by photographic assessment in the study eye at both timepoints.

^c P-values are on the differences between KPI-121 and vehicle by t-test on difference of adjusted least square means on observed score from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

^d P-values are on the difference between KPI-121 and vehicle by t-test on difference of adjusted least square means on change from baseline from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

Source: [Tables 14.2.1.1.1 and 14.2.1.1.2](#)

At Day 29 (primary timepoint), the mean bulbar conjunctival hyperemia score as determined by photographic assessment of the worst region (determined at baseline) of the study eye was 1.4 in the KPI-121 0.25% group compared with 1.6 in the vehicle group. The between-group difference was statistically significant, favoring KPI-121 0.25% over vehicle (p = 0.039).

Table 8 -Summary of Modified SANDE Severity Scores for the 7-day Average Prior to Visit (ITT Population) KPI-121-C-002

	KPI-121 0.25% (N = 73)	Vehicle (N = 77)	Between-group Difference p-value ^a
Baseline^b			
n	73	77	
Mean (SD)	66.82 (15.126)	67.63 (13.321)	
Median	67.43	68.14	
Min, Max	12, 94	30, 96	
Day 15 (Observed)^b			
N	72	77	
Mean (SD)	58.83 (20.745)	63.63 (17.844)	-4.12 0.1072 ^c
Median	63.00	65.43	
Min, Max	2, 95	6, 98	
Day 15 (Change From Baseline)^b			
N	72	77	
Mean (SD)	-7.96 (17.344)	-3.99 (13.591)	-4.12 0.1072 ^d
Median	-3.14	-2.00	
Min, Max	-78, 28	-61, 26	
Day 29 (Observed)			
N	73	77	
Mean (SD)	57.05 (23.892)	60.47 (19.770)	-2.64 0.3764 ^e
Median	63.71	60.14	
Min, Max	3, 97	6, 97	
Day 29 (Change From Baseline)			
N	73	77	
Mean (SD)	-9.77 (21.422)	-7.16 (14.512)	-2.64 0.3764 ^d
Median	-6.43	-5.86	
Min, Max	-71, 26	-63, 27	

Note: Modified SANDE Severity Scores were calculated based on the average 7-day score prior to the visit. Day 29 is the primary timepoint.

^a P-values are 2 sided; significance level is 0.05. Between-group differences are for KPI-121 minus vehicle, where negative values favor KPI-121.

^b Day 15 was evaluated as a secondary endpoint (see [Section 11.2.8](#)), but is presented alongside the results for the primary endpoint (Day 29) to provide a complete summary of Modified SANDE Severity scores at both timepoints.

^c P-values are on the difference between KPI-121 and vehicle by t-test on difference of adjusted square means square on observed value from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

^d P-values are on the difference between KPI-121 and vehicle by t-test on difference of adjusted square means square on change from baseline from ANCOVA with treatment and randomized stratum as fixed factors and baseline score as a covariate in the model.

Source: [Tables 14.2.3.1](#) and [14.2.3.2](#)

For Modified SANDE Severity Scores, using the mean of scores over the 7 days prior to the Day 29 visit, the results were numerically better in the KPI-121 0.25% group (57.1 mm) compared with the vehicle group (60.5 mm), but they were not statistically significant (p = 0.38).

6.2. Trial KPI-121-C-006

A Phase 3, Double-masked, Randomized, Controlled Study of KPI-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease

6.2.1. Study Design

Overview and Objective

The primary objective of the study was to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects who had a documented clinical diagnosis of dry eye disease.

Trial Design

This was a Phase 3, multicenter, double-masked, randomized, vehicle-controlled, parallel-group study designed to evaluate the safety and efficacy of KPI-121 0.25% ophthalmic suspension in treating the signs and symptoms of dry eye disease. This study included up to 4 clinic visits, including 2 weeks of single-masked vehicle run-in followed by up to 2 weeks of study treatment dosing (KPI-121 0.25% ophthalmic suspension or vehicle).

Approximately 2000 subjects at approximately 60 centers located in the US were planned to be evaluated for eligibility at Screening. Subjects meeting eligibility criteria at Screening (Visit 1) entered a 14 ± 1 day run-in period of four times daily (QID) dosing with single-masked vehicle in both eyes. On Day 1 (Visit 2), subjects who continued to meet eligibility criteria were randomized in an approximate 1:1 ratio to either KPI-121 0.25% ophthalmic suspension or vehicle dosed QID in both eyes. Subjects returned to the clinic at Day 8 (± 1 day; Visit 3) to review diary data, evaluate eye dryness, and report concomitant medication use and adverse events (AEs). Subjects returned to the clinic at Day 15 (± 1 day; Visit 4) for a complete study evaluation, discontinuation of dosing, and study exit. Bottles of study treatment were dispensed at designated visits based on the subject's randomization.

Randomization was stratified at baseline based on study qualification criteria entered into the interactive web recognition system (IWRS), as follows:

- Ocular discomfort severity (ODS) scores of low (> 40 mm to < 68 mm) or high (≥ 68 mm to 100 mm) based on the subject's rating of ODS on the day prior to Day 1; and
- Investigator-rated bulbar conjunctival hyperemia scores of low (2) or high (≥ 3) in the eye with the higher score at Day 1.

Table 9 - Summary of Procedures KPI-121-006

Procedures	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	Randomization	Diary Collection Visit	End of Study Visit
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)
Informed Consent, HIPAA Authorization and Significant Medical History	X			
Subject-rated assessment of ocular discomfort (in office)	X			
Subject-rated assessment of ocular discomfort (subject diary)		X ^c	X ^c	X ^c
Subject-rated assessment of eye dryness (in office)		X	X	X
Concomitant medication query	X	X	X	X
Urine pregnancy test ^a	X			X
Inclusion/Exclusion	X	X		
AE Assessment	X	X	X	X
Investigator-rated assessment of bulbar conjunctival hyperemia	X	X		X
Bulbar conjunctival hyperemia photography		X		X
BCVA	X	X		X
Slit lamp biomicroscopy	X	X		X
Corneal fluorescein staining	X	X		X
Unanesthetized Schirmer Test Assessment	X			
IOP measurement	X	X		X
Dilated ophthalmoscopy	X			X
Study treatment administration in-clinic	X ^b	X		
Dispense study product	X ^b	X		
Dispense subject diary	X ^b	X	X	
Collect study product		X ^b		X
Collect subject diary		X ^b	X	X

AE = adverse event; BCVA = best corrected visual acuity; HIPAA = Health Insurance and Portability and Accountability Act; IOP = intraocular pressure

^a women of child bearing potential only

^b run-in product

^c collected through use of subject diary

Study Endpoints KPI-121-006

The trial had 4 primary efficacy endpoints:

2 ocular sign endpoints

- Change from baseline in conjunctival hyperemia scores at the Day 15 visit, in the intent-to-treat (ITT) population
- Change from baseline in inferior corneal staining scores at the Day 15 visit, in the ITT

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population

and 2 ocular symptom endpoints

- Change in ODS scores from Day 1 to Day 15 using mean scores for the 3 days prior to the study day, in the ITT population
- Change in ODS scores from Day 1 to Day 15 using mean scores for the 3 days prior to the study day, in the ITT subgroup with ODS scores ≥ 68 mm 1 day prior to Day 1.

These 4 endpoints were analyzed in 2 separate testing sequences utilizing a parallel gatekeeping method with recycling of unspent alpha (based on FDA draft guidance Multiple Endpoints in Clinical Trials, January 2017). Each sequence was tested in a hierarchal manner at a significance level of 0.025.

Inclusion/Exclusion Criteria KPI-121-C-006

Inclusion/Exclusion Criteria were Identical to criteria for Trial KPI-121-C-002.

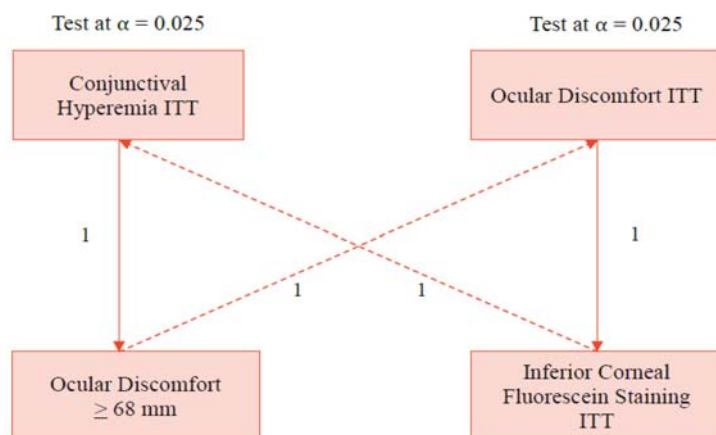
Investigational Products KPI-121-C-006

Investigational Products were Identical to those used in Trial KPI-121-C-002.

Statistical Analysis Plan KPI-121-C-006

All primary efficacy endpoint comparisons were performed between the KPI-121 0.25% ophthalmic suspension group and the vehicle group using a parallel gatekeeping method with recycling of unspent alpha.

Figure 1 - Parallel Gatekeeping Method with Recycling of Unspent Alpha KPI-121-C-006



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Investigators KPI-121-C-006

Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
137	Marc Abrams, MD, PhD	None	Abrams Eye Center 2322 E. 22nd Street, Suite 102 Cleveland, OH 44115	50(45)
163	Carol Aune, OD	Kim Major-Walker, RN Craig Stevens, MD	Eyecare Center 4170 Fayetteville Road Raleigh, NC, 27603	103(39)
141	Jason Bacharach, MD	Lisa Teel, OD Angela Lewis Reynolds Celeste Campbell Maria Suarez Rebecca Craig	North Bay Eye Associates, Inc. 104 Lynch Creek Way, Petaluma, CA 94954	33(5)
164	Laurie Barber, MD	None	Little Rock Eye Clinic, LLP 201 Executive Court, Suite A Little Rock, AR, 72205	16(7)
126	Gregg J. Berdy, MD, FACS	Ranjan Malhotra, MD Robert C. Brusatti, OD Andrew Royer, OD Debi Gravemann, RN Dawn Wiemers	Ophthalmology Associates 12990 Manchester Road Suite 200 St. Louis, MO 63131	37(11)
142	Mark T. Bergmann, MD	Daniel J. Hammer, MD Barbara B. Henry, CCRC Natalie Carpenter	Apex Eye 6507 Harrison Avenue. Suite E Cincinnati, OH 45247	39(13)
193	Lance Bergstrom, MD	Nicole M. Collins, OD Tracie T. Malsom, OD Kristen N. Peterson, CCRC	Bergstrom Eye Research 2601 South University Drive Fargo, ND, 58103	5(0)
167	Robert L. Berry, MD	None	Eyecare Arkansas, P.A. 9800 Baptist Health Drive, #301, Little Rock, AR, 72205	3(3)
143	James Boyce, MD	Norman Liu, MD Ryan Taban, MD Gladys Sager CCRC	Orange County Ophthalmology Medical Group 12665 Garden Grove Blvd, #401 Garden Grove, CA 92843	43(36)
165	Y. Ralph Chu, MD	Jessica N. Heckman, OD Marc Harrie, OD	Chu Vision Institute 9117 Lyndale Avenue South Bloomington, MN, 55420	5(1)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
239	Deepinder Kaur Dhaliwal, MD	Ladan Espander, MD Alex Mammen, MD Vishal Jhanji, MD Jackie Fisher Rhonda Dahlstrom Melessa Salay	University of Pittsburg School of Medicine- Dept of Ophthalmology UPMC Eye Center 203 Lothrop Street Pittsburgh, PA, 15213	19(3)
216	El-Roy Dixon, MD	Shawn Wynn Bettina A. Barfield Jennifer Underwood	Dixophthal, P.C. dba Dixon Eye Care, 806 North Jefferson Street Albany, GA, 31701	5(4)
166	Daniel Durrie, MD	Timothy P. Lindquist, MD Christopher J. Pole, MD Kelly F. Grosdidier, OD Michele R. Avila, OD Suzanne R. LaKamp, OD Teresa Nolan Shari D. Clark Cindy Smith	Durrie Vision 5520 College Boulevard Suite 201 Overland Park, KS, 66211	(0)0
104	Alice Epitropoulos, MD	Megan M. Chambers, MD	The Eye Center of Columbus/Ophthalmic Surgeons & Consultants of Ohio 262 Neil Avenue, Suite # 430 Columbus, OH 43215	28(6)
127	David Evans, OD	Eugene McLaurin, MD Don Gayso, OD Brandon J. Rushing, OD Nelson Carney Amelia Murray Sarina Donahue Daniel J. Ashe Kim Smith Nick Leal Sean Hannahan	Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	86(45)
176	Richard Evans, MD	Jason Burns, MD Michael A. Orozco, OD Brian Matthews Catherine Alderete	Keystone Research - Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX, 78240	37(16)
181	Brad Feldman, MD	Mark H. Blecher, MD Carolyn S. Repke, MD Marc D. Garden, MD William Canale Kelleanne Curran, CCRC Steve Warner Lisa Flynn, CCRC Shante Washington	Philadelphia Eye Associates 1703 South Broad Street Philadelphia, PA, 19148	(0)0
217	Asra Shabana Firozvi, MD	James Milton, MD Tameka Cooper Jackquelyne Bell	North Carolina Eye, Ear, Nose & Throat (Firozvi Research, LLC) 4102 N. Roxboro Road, Durham, NC, 27704	22(18)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
169	Bret L. Fisher, MD	Gene Wong, OD Delania Robinson Carin Zachman Juanita Thompson Paul McGoey	The Eye Center of North Florida 2500 Martin Luther King, Jr. Boulevard Panama City, FL, 32405	0(0)
218	S. Lance Forstot, MD, FACS	Richard Damiano, MD Robert Fish, MD Karen Repine, MD Dana Damiano Kelly Hammer	Corneal Consultants of Colorado 8381 Southpark Lane Littleton, CO, 80209	23(18)
106	Joseph Gira, MD	Michael Donahoe, MD Erin Sullivan, OD Amy Young Stephanie Williams	Ophthalmology Consultants Ltd. 12990 Manchester Road Suite 201 St. Louis, MO 63131	33(16)
230	John D. Goosey, MD	Jeffery B. Arnoult, MD Stephanie Verkin CRC, Santa Montelongo, CRC Caroline Beard, CRC Ayesha Pervaiz, CRC Norma A. DelBosque Naina Sudarshan, Eunhea Grace Pei Alnaserbelh AlNaseri, CRC	Houston Eye Associates 2855 Gramercy Street Huston, TX, 77025	26(13)
219	Jack Greiner, DO	Paula Oliver	Clinical Eye Research of Boston 955 Main Street, Suite 307 Winchester, MA, 01890	22(9)
220	Charlene Grice, MD	Jeffrey F. Hood, OD Krissa L. Drentlaw, COT Helga P. Sandoval, MD Clarissa A. Harps, COT	Carolina Eyecare Physicians, LLC 1101 Clarity Road Suite 100 Mt. Pleasant, SC, 29464	0(0)
148	Robert H. Gross, MD	Jung T. Dao, MD Julie Komer Kristine Zakrzewski	Cornea and Cataract Consultants of Arizona 3815 E. Bell Road, Suite 2500 Phoenix, AZ 85032	30(21)
168	Mohammad Ali Haider, DO	Ashley Griffith, BS Sheeraz Naqvi, BS Susan Brown Jennifer Yarbor	Senior Health Services 2932 Breckenridge Lane Suite 5 Louisville, KY, 40220	60(43)
108	Paul J. Hartman, MD	Alan H. Gruber, MD Howard I. Schenker, MD Mindy VanVoorhis, CCRC Melissa Hart, CCRC Michelle Hurley, COA Rachel Rivera	Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618	58(18)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
229	Khoa Hoang, MD	Rajesh K. Rajpal, MD Dawn Williams, OD Christine Wisecarver, OD	See Clearly Vision 8138 Watson Street McLean, VA, 22102	2(0)
151	Mitchell Jackson, MD	Maggie Sawa	Jackson Eye, SC 300 N Milwaukee Ave, Suite L Lake Villa, IL, 60046	34(15)
178	Janet Kim, MD	Jennifer Hung, MD	Montebello Medical Center, Inc. 229 E. Beverly Boulevard, Montebello, CA, 90640	24(13)
170	Alexandra Kostick, MD, FRCSC, FACS	None	Atlantic Eye Center 3 Pine Cone Drive Suite 104 Palm Coast, FL, 32137	25(0)
247	Thomas LoBue, MD	Ryan G. Miller, OD Stephen A. LoBue, MD	LoBue Laser and Eye Medical Center, 40700 California Oaks Road, Suite 106 Murrieta, CA 92562	12(2)
132	Jodi I. Luchs, MD, FACS	Jason Todd Flicker, MD Howard Adam Lane, MD Michelle Go Mijares, OD Cara Fidnarick, CCRC Debora Losito, COA, CRC Mary Modica, CRC	South Shore Eye Center, LLP 2185 Wantagh Avenue Wantagh, NY 11793	44(25)
196	Benjamin Marske, OD	Karl Olsen, MD Marti Jo Chavez Natalie Santelli, OD Marcelo Saldivia, OD	Eye Center of Northern Colorado 1725 East Prospect Road Ft. Collins, CO, 80525	2(0)
111	Joseph Ruben Martel, MD	Martha Orozco Cortes Nastya Padure Diana Petrashishin Unsa Anwar	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670	82(44)
221	Cynthia Matossian, MD, FACS	Janune Disanti, OD Travis Gabriel, OS Sebastian Lesniak, MD Joan Micucci, COMT Aleisha Morosco Erin Murphy, COA Kristina Farley, COT Melissa Mazzocchi, COA	Matossian Eye Associates 2 Capital Way Suite 326 Pennington, NJ, 08534	20(6)
171	Edward Meier, MD	Kelly P. O'Neill, MD Tina M. Winward, COA Christina M. Hughes, COA Kelsey Barker Natalie Carpenter	Apex Eye 6394 Thornberry Court Unite 810 Mason, OH, 45040	75(17)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
129	Mark Milner, MD	Robin Kwoka	Eye Center of Southern CT, PC 2880 Old Dixwell Avenue Hamden, CT 06518	0(0)
172	Thomas Mundorf, MD	Michelle Mundorf Kelsey Seretis Golbahar Mohseni Allison Dean	Mundorf Eye Center 1718 East Fourth Street Suite 703 Charlotte, NC, 28204	3(1)
155	James H. Peace, MD	Shohreh Neshat Daisy Hernandez Feliks Sinyak Arnold Penarroyo Rania Bara Carmelina Marin	United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	40(30)
173	Robert B. Pendleton, MD, PhD	Victor Wechter, MD Debra McCluskey Diana Amador Yadira Topping Genessis Guzman	Pendleton Eye Center 3637 Vista Way Oceanside, CA 92056	22(7)
238	Mujtaba Qazi, MD	Jay S. Pepose, MD Steven Branstetter, OD James Rieger, OD Lee Stolze Roxanne Canter Tiffany McNeill	Lifelong Vision Foundation at Pepose Vision Institute 1815 Clarkson Road Chesterfield, MO, 60317	6(1)
130	Steven H. Rauchman, MD	Robert John Smyth Medina, MD Joanne Perry Rocio Rodriguez Denise Nunez Wendy Torres Rocio Garcia Elise Levine	North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	95(36)
174	Vincent A. Restivo, Jr., MD	Mark P. Welding, OD Sheila Nardelli, COA, MMSc Beverly Dvorak	Hill Country Eye Center 11901 West Parmer Lane, Suite 400 Cedar Park, TX, 78613	45(32)
175	Kyle Murphy Rhodes, MD	Julie Gron, OD	Lake Travis Eye and Laser Center 401 Ranch Road 620, Suite 210 Lakeway, TX, 78734	77(39)
139	Robert Alan Rice, MD	William John Flynn, MD Edward Raymond Rashid, MD Charles Daniel Reilly, MD Catherine Hazen Griselda Rodriguez Lauren Ortega Tracy Rodriguez	R and R Eye Research, LLC 5430 Fredericksburg Rd Suite 100 and 120 San Antonio, TX 78229	60(5)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
222	Trent D. Richards, MD	Larence M. Nelson, MD Collind Boyington, CRC Dennis Cinquegrani, Jr., BS, CRC Melanie Gibb, CCRC Stephanie Smith, CRC	Tanner Clinic 1756 W. Antelope Dr. Layton, UT, 84041	33(8)
177	Jay Michel Rubin, MD	Marcie Smith Lori Colon	Eye Clinics of South Texas 999 E. Basse Road Suite 128-B San Antonio, TX, 78209	33(18)
118	Kenneth Sall, MD	Julie Kim, OD Jade Davis, OD Leticia Guzman, CCRC Cindy Lee, CCRC Ilanie Shiell, CCRC Patricia Manjarrez, CCRC	Sall Research Medical Center, Inc. 11423 187th Street Suite 200 Artesia, CA 90701	78(47)
231	Barry Alan Schechter, MD	None	Florida Eye Microsurgical Institute 1717 Woolbright Road Boynton Beach, FL, 33426	10(6)
179	Robert L. Schultze, MD, FACS	Alice Titova, COA Melissa Brennan Melissa Delap Michael Joseph Cortese, OD Jennifer Marie Grill, OD, FAAO	Cornea Consultants of Albany, PLLC 9 Vista Boulevard Suite 100 Slingerlands, NY, 12159	5(1)
199	Jay Lawrence Schwartz, OD	Marc R. Bloomenstein, OD Katie O'Brien, COA	Schwartz Laser Eye Center 8416 E. Shea Boulevard Suite C-101 Scottsdale, AZ, 85260	20(1)
157	Philip Lee Shettle, DO	None	Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	15(13)
180	Patricia B. Sierra, MD	Samuel H. Lee, MD Monica C. Robinson, OD	Sacramento Eye Consultants 1515 River Park Drive Suite 100 Sacramento, CA, 95815	21(6)
200	David Irving Silbert, MD, FAAP	None	Conestoga Eye 2104 Spring Valley Road Lancaster, PA, 17601	36(7)
159	Stephen E. Smith, MD	Angela R. Kaplan, OD Ginger Marinell Monica Rumble	Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL, 33901	27(11)
240	Terrence S. Spencer, MD	Stephen Seth Khachikian, MD Monte S. Dirks, MD Kayla Riley, CRC	Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD, 57701-7394	26(9)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
201	Clark Springs, MD	Blair Boehmer, MD Mary Adams Tammy Dale	Midwest Cornea Associates, LLC 10300 North Illinois Street Suite 1020 Indianapolis, IN, 46290	41(17)
223	Michael Craig Stiles, MD	Ann Stechschulte, MD Amanda Strom, OD Lindsay Lankford, CRC, COA Whitney Tuttle	Stiles EyeCare Excellence and Glaucoma Institute PA 7200 W. 129th Street Overland Park, KS, 66213	7(5)
232	Vance Thompson, MD	John Berdahl, MD Alison Tendler, MD Douglas Wallin, OD Keith Rasmussen, OD Justin Schweitzer, OD Mitch Ibach, OD Jason Schmit, OD Keeley Puls Kristin Ford Samantha Nielson Melissa Holm	Vance Thompson Vision 3101 W 57th Street Sioux Falls, SD, 57108	9(0)
182	Da-Thuy Van, DO	Bernard A. Milstein, MD Chance Caddell Angie Carter	The Eye Clinic of Texas, an affiliate of Houston Eye Associates 1100 Gulf Freeway, Suite 114 League City, TX, 77573	50(14)
202	Kent L. Wellish, MD	Jay Kenneth Mattheis, MD Issac Ortiz, OD Alexander Choy, OD	Wellish Vision Institute 2110 East Flamingo Road Suite 210, 211 Las Vegas, NV, 89119	79(10)
162	Jon-Marc Weston, MD, FACS	Gregory M. Valle, OD Steven F. Tronnes, OD Deborah M. Harding, COT Shantelle Weakley, CCRC, COA	Roseburg Research Associates, LLC 2435 NW Kline Street Roseburg, OR, 97471	12(1)
215	David Wirta, MD	David Salvay, MD Linda Wirta Yvette Abbascia Heather Tyner Kimberly Abbascia Haley Noel Mai Giang Jenny Ryan Taylor Fogarty Shelby Buckley William Kiely Tina Johns	Eye Research Foundation 520 Superior Avenue Suite 235 Newport Beach, CA, 92663	84(45)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
233	Elizabeth Yeu-Lin, MD	Jay Starling, MD Walter Whitley, OD	Virginia Eye Consultants 2020 General Booth Boulevard Virginia Beach, VA, 23454	4(0)
224	Daniel V. Zimmer, MD, FACS	Derek W. O'Donnell, OD Marjorie Lopiccolo, CRC	Scott & Christie and Associates, PC 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066	38(36)

6.2.2. Study Results KPI-121-C-006

Compliance with Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Financial Disclosure

See Appendix 13.2 of this review.

Patient Disposition KPI-121-C-006

	KPI-121 0.25% (N = 459)	Vehicle (N = 456)	Total (N = 915)
Completed Study	455 (99.1%)	453 (99.3%)	908 (99.2%)
Subjects Withdrawn Early from the Study	4 (0.9%)	3 (0.7%)	7 (0.8%)
Reason for Study Exit			
Withdrawal by subject	3 (0.7%)	1 (0.2%)	4 (0.4%)
Adverse event	0	0	0
Pregnancy	0	0	0
Physician decision	0	0	0
Lost to follow-up	0	0	0
Other	1 (0.2%)	2 (0.4%)	3 (0.3%)

ITT = intent to treat

Source: Table 14.1.2.1

A total of 2054 subjects were screened for the study; of these, 1136 were screening or randomization failures (i.e., subjects who failed to meet eligibility criteria at Visit 1 and/or at Visit 2) and 918 were screen successes and were randomized into the trial. Included in these 918 randomized subjects were 2 individuals who enrolled in the study twice at 2 different sites and 1 individual who completed the other phase 3 trial, KPI-121-C-007, and then enrolled in this trial. The second-participation data for these 3 individuals (Subject IDs (b) (6))

(b) (6) were not included in any analysis population. Thus, 915 subjects were eligible to be included in the analysis populations of the study.

Additionally, during monitoring of this study, it was discovered that 1 site (Site 170) initiated subjects' treatment with study treatment (KPI-121 or vehicle) at Visit 1, without first completing the protocol-mandated 14 ± 1 -day run-in period with vehicle and without randomizing the subjects in IWRS. Twenty-five subjects received study treatment at this site for up to 2 weeks. Upon discovery of this issue, Kala discontinued the affected subjects from the trial and closed the site. None of the 25 subjects had adverse events. They were only seen at Screening and early termination. With FDA agreement (pre-NDA meeting minutes issued 29 Aug 2017), data from Site 170 were excluded from all analysis populations.

Protocol; Violations/Deviations KPI-121-C-006

	KPI-121 0.25% (N = 459)	Vehicle (N = 456)	Total (N = 915)
Completed Study	455 (99.1%)	453 (99.3%)	908 (99.2%)
Subjects Withdrawn Early from the Study	4 (0.9%)	3 (0.7%)	7 (0.8%)
Reason for Study Exit			
Withdrawal by subject	3 (0.7%)	1 (0.2%)	4 (0.4%)
Adverse event	0	0	0
Pregnancy	0	0	0
Physician decision	0	0	0
Lost to follow-up	0	0	0
Other	1 (0.2%)	2 (0.4%)	3 (0.3%)

ITT = intent to treat

Source: [Table 14.1.2.1](#)

See "Patient Disposition KPI-121-C-006" above in this review regarding Site 170.

Table of Demographic Characteristics

Table 10 - Demographic Characteristics KPI-121-C-006

	KPI-121 0.25% (N = 459)	Vehicle (N = 456)	Total (N = 915)
Age (years)			
Mean	58.1	58.3	58.2
SD	15.41	14.66	15.03
Median	60.0	60.5	60.0
Min, Max	18, 90	19, 88	18, 90
Gender, n (%)			
Male	92 (20.0)	97 (21.3)	189 (20.7)
Female	367 (80.0)	359 (78.7)	726 (79.3)
Ethnicity, n (%)			
Hispanic/Latino	65 (14.2)	76 (16.7)	141 (15.4)
Not Hispanic/Latino	394 (85.8)	380 (83.3)	774 (84.6)
Race, n (%)			
American Indian/Alaskan Native	2 (0.4)	0	2 (0.2)
Asian	18 (3.9)	18 (3.9)	36 (3.9)
Black/African-American	69 (15.0)	71 (15.6)	140 (15.3)
Native Hawaiian/Other Pacific Islander	1 (0.2)	1 (0.2)	2 (0.2)
White	362 (78.9)	361 (79.2)	723 (79.0)
Unknown	0	0	0
Other Race	6 (1.3)	4 (0.9)	10 (1.1)
Mixed	1 (0.2)	1 (0.2)	2 (0.2)

ITT = intent to treat; Max = maximum; Min = minimum; SD = standard deviation

Source: [Table 14.1.4](#)

The 915 subjects in the ITT and safety populations were predominantly female (79%) and white (79%), with a mean (range) age of 58.2 (18 to 90) years. No meaningful differences were observed between the treatment groups in terms of demographic characteristics.

Efficacy Results – Primary Endpoints KPI-121-C-00

Table 11 - Summary of Primary Efficacy Results KPI-121-C-006

Primary Endpoint (Population)	KPI-121 0.25% (N = 459)		Vehicle (N = 456)		Trt Diff p-value ^a
	Day 1	Change at Day 15	Day 1	Change at Day 15	
Ocular signs					
Conjunctival hyperemia scores ^b at the Day 15 visit (ITT, mean [SD])	n = 458 1.9651 (0.60168)	n = 452 -0.4049 (0.65062)	n = 455 1.9692 (0.61831)	n = 451 -0.1574 (0.60704)	-0.25 < 0.0001
Inferior corneal staining scores ^c at the Day 15 visit (ITT, mean [SD])	n = 459 2.1 (0.70)	n = 455 -0.5 (0.84)	n = 455 2.1 (0.66)	n = 452 -0.4 (0.79)	-0.08 0.1128
Ocular symptoms					
ODS scores ^d at Day 15 (ITT, mean [SD])	n = 459 68.93 (15.888)	n = 455 -14.53 (20.636)	n = 456 69.26 (15.378)	n = 452 -9.16 (17.924)	-5.43 < 0.0001
ODS scores ^d at Day 15 (ITT subgroup with ODS scores ≥68 mm 1 day prior to Day 1, mean [SD])	n = 260 79.38 (10.062)	n = 257 -16.67 (21.937)	n = 264 79.26 (9.741)	n = 264 -10.76 (18.037)	-5.90 0.0009

ITT = intent to treat; ODS = ocular discomfort severity; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle) using least-square means

^a P-values were calculated based on an analysis of covariance with baseline value as covariate and treatment group and randomization strata as fixed effects.

^b Conjunctival hyperemia scores (using the CCLRU grading scale, from 0 [none] to 4 [severe]) were based on masked photographic assessments conducted at a central photographic reading center, in the worst region of the study eye. The study eye and the worst region were defined using an algorithm described in the statistical analysis plan.

^c Inferior corneal staining scores (using the NEI scale, from 0 to 3) in the study eye were based on evaluations by the investigator. The study eye was defined using an algorithm described in the statistical analysis plan.

^d ODS scores (from 0 to 100 mm) were derived from data entered into diaries by subjects. Scores were general evaluations across both eyes; there were not separate questions for each eye. Higher scores indicate more severe ocular discomfort. Three-day means were calculated using available data from the 3 days prior to Day 15 (regardless of when Visit 4 [ie, the Day 15 visit] occurred) and the 3 days prior to Day 1. Only available data are used without imputation; if the target number of prior days of diary data was not available, the number of days contributing to the average could be less than the target.

Source: Tables 14.2.1.1, 14.2.1.7, 14.2.1.9, and 14.2.1.12

For all endpoints, a negative change indicated an improvement in the sign or symptom being measured. Statistically significant results favoring KPI-121 0.25% over vehicle were observed for 3 of the 4 primary endpoints defined for this study. For inferior corneal staining scores, the between-group difference in change from baseline at the Day 15 visit was -0.08, favoring KPI-121 0.25% over vehicle, but not reaching statistical significance (p = 0.11).

6.3. Trial KPI-121-C-007

A Phase 3, Double-Masked, Randomized, Controlled Study of Kpi-121 0.25% Ophthalmic Suspension Compared to Vehicle in Subjects with Dry Eye Disease

6.3.1. Study Design

Overview and Objective

The primary objective of the study was to investigate the safety and efficacy of KPI-121 0.25% ophthalmic suspension compared to vehicle in subjects who had a documented clinical diagnosis of dry eye disease.

Trial Design

The trial design was essentially Identical to Trial KPI-121-C-006 although the study endpoints were different. See below in this review Section for Study Endpoints.

Table 12 - Summary of Procedures KPI-121-C-007

Procedures	Visit 1	Visit 2	Visit 3	Visit 4
	Screening	Randomization	Diary Collection Visit	End of Study Visit
	14 ± 1 Days Prior to Day 1	Day 1	Day 8 (±1 day)	Day 15 (±1 day)
Informed Consent, HIPAA Authorization and Significant Medical History	X			
Subject-rated assessment of ocular discomfort (in office)	X			
Subject-rated assessment of ocular discomfort (subject diary)		X ^c	X ^c	X ^c
Subject-rated assessment of eye dryness (in office)		X	X	X
Concomitant medication query	X	X	X	X
Urine pregnancy test ^a	X			X
Inclusion/Exclusion	X	X		
AE Assessment	X	X	X	X
Investigator-rated assessment of bulbar conjunctival hyperemia	X	X		X
Bulbar conjunctival hyperemia photography		X		X
BCVA	X	X		X
Slit lamp biomicroscopy	X	X		X
Corneal fluorescein staining	X	X		X
Unanesthetized Schirmer Test Assessment	X			
IOP measurement	X	X		X
Dilated ophthalmoscopy	X			X
Study treatment administration in-clinic	X ^b	X		
Dispense study product	X ^b	X		
Dispense subject diary	X ^b	X	X	
Collect study product		X ^b		X
Collect subject diary		X ^b	X	X

AE = adverse event; BCVA = best corrected visual acuity; HIPAA = Health Insurance and Portability and Accountability Act; IOP = intraocular pressure

^a women of child bearing potential only

^b run-in product

^c collected through use of subject diary

Study Endpoints KPI-121-C-007

The trial had 2 primary efficacy endpoints:

1. One ocular sign endpoint: Change from baseline in conjunctival hyperemia scores at the Day 15 visit in the intent-to-treat (ITT) population
2. One ocular symptom endpoint: Change in ODS scores from Day 1 to Day 15 using mean scores for the 3 days prior to the study day in the ITT population.

Each primary endpoint was tested independently using an alpha of 0.025. A Bonferroni correction was applied to the primary efficacy analysis, to correct for multiplicity.

- Conjunctival Hyperemia: Change from baseline (Day 1) in bulbar conjunctival hyperemia scores in the ITT population at the Day 15 visit in the region of worst severity of bulbar conjunctival hyperemia (as defined based on Day 1 photographs) in the study eye, based on masked photographic assessment conducted at a central photographic reading center.
- ODS: Change in ODS scores in the ITT population calculated as the mean of the scores recorded in the subject's diary for the 3 days prior to Day 15 minus the mean of the scores for the 3 days prior to Day 1.

Inclusion/Exclusion Criteria KPI-121-C-007

Inclusion/Exclusion Criteria were Identical to criteria for Trial KPI-121-C-002 and -006.

Investigational Products KPI-121-C-007

Investigational Products were Identical to those used in Trial KPI-121-C-002 and -006.

Statistical Analysis Plan KPI-121-C-007

The intent-to-treat (ITT) population was defined as all randomized subjects who received at least 1 dose of randomized study treatment. The subjects were analyzed as randomized, ie, according to the planned treatment. Each primary endpoint was tested independently using an alpha of 0.025. A Bonferroni correction was applied to the primary efficacy analysis, to correct for multiplicity.

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Investigators

Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
138	Jack Abrams, MD	Tapan R. Shah, MD Beth Kimball, RN Lindsey B. Kowal	Abrams Eye Institute 6450 Medical Center St. #100 Las Vegas, NV 89148	63(31)
140	Louis M. Alpern, MD	Terri Cintron	The Cataract & Glaucoma Center 4171 N. Mesa Building D100 El Paso, TX 79902	41(25)
225	Kenneth Beckman, MD, FACS	George Chioran, MD Steven Suh, MD Ashley George Danielle Flading Donna Coury Angela Robinson Tammy Altizer	Comprehensive Eye Care of Central Ohio 450 Alkyre Run Drive, Suite 100 Westerville, OH, 43082	4(0)
143	James Boyce, MD, FACS	Norman Liu, MD Ryan Taban, MD Gladys Sager CCRC	Orange County Ophthalmology 12665 Garden Grove Boulevard, Suite 401 Garden Grove, CA 92843	54(31)
183	James D. Branch, MD	Kelly Marvin Danielle Cox Cathy Revis, COA Marcie Harrington	James D Branch MD 224 Town Run Lane, Winston-Salem, NC, 27101	17(10)
203	Frank Bucci, MD	Louis Moriano, OD	Bucci Laser Vision Institute 158 Wilkes-Barre Township Boulevard, Wilkes-Barre, PA, 18702	9(5)
184	Leonard R. Cacioppo, MD	None	Hernando Eye Institute 14543 Cortez Boulevard, Brooksvill, FL, 34613	40(15)
102	Robert DaVanzo, MD	Michael E. Tepedino, MD J. Zachary Forsey, MD Michael W. Evans, MD	Cornerstone Eye Care 1400 East Hartley Drive High Point, NC 27262	30(16)
146	Michael Depenbusch, MD	Anita Schadlu, MD Gerald B. Walman, MD Deepthi Rao, MD Erin Burk, MS Mallory Barker, MS Jerry Tolle, Jr. Gina Klingelhoets	Arizona Eye Center 1500 W. Ray Road, Chandler, AZ, 85224	64(18)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
136	Harvey DuBiner, MD	Ronald Weber, MD Daniel I. Strait, OD Carey Phlong, OD Peter Chen, OD, PhD Brenton D. Smith, OD Robert Smith, CCRC Ethan Seville, CCRC Heather Ambrosia, OD Helen DuBiner, PharmD, Thuy Ngo Melissa Byrd Hannah Davis	Eye Care Centers Management, Inc. (Clayton Eye Center) Suite 120 1000 Corporate Center Drive, Morrow, GA, 30260	18(4)
147	Sherif M. El-Harazi, MD	Kay Park, MD Lilit Minasyan, MD Abed Namavari, MD	Lugene Eye Institute 1510 South Central Avenue, #300 Glendale, CA 91204	74(42)
127	David Evans, OD	Eugene McLaurin, MD Don Gayso, OD Brandon J. Rushing, OD Isaiah Choy Nelson Carney Amelia Murray James Patrick Harrison Sarina Donahue Daniel J. Ashe Kim Smith Ariel Kalafat Nick Leal	Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	74(45)
204	Marjan Farid, MD	Sumit Garg, MD Matthew Wade, MD	The Gavin Herbert Eye Institute 850 Health Science Road, Irvine, CA, 92697	1(1)
105	Raymond Fong, MD	Douglas B. Friedrich, MD Albert Yuen Jenny Kam Yat Yoong Kok Kian Yek Kok Pow Yee Kok	Raymond Fong, MDPC 109 Lafayette Street, 4 th Floor New York, NY 10013	61(30)
236	Nicole Fram, MD	Samuel Masket, MD	Advanced Vision Care 2080 Century Park East, Suite 911 Los Angeles, CA, 90067	1(1)
237	Emily Shull, MD	Albert Cheung, MD Rachel Crabtree, COA Elizabeth Wright	Cincinnati Eye Institute 580 South Loop Road Suite 200 Edgewood, KY, 41017	28(2)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
107	Damien Goldberg, MD	Barry Wolstan, MD	Wolstan & Goldberg Eye Associates 23600 Telo Avenue, Suite 100 Torrance, CA 90505	45(23)
242	Jonathan P. Grady, MD	Frank J. Grady, MD	Brazosport Eye Institute/Frank J. Grady, M.D. & Associates 103 Parking Way, Lake Jackson, TX, 77566	14(8)
150	David Hardten, MD, FACS	Ahmad Fahmy, OD Alyson L. Blakstad, OD Kate A. Montealegre, OD Sonja E. Iverson-Hill, OD Gina Doeden, OD Johnna Hobbs, OD Mona Fahmy, OD Alicia Alvarado, OD Lindsey Fallenstein Erich Berg Emily Eskola Robert Wroblewski	Minnesota Eye Consultants, PA 10709 Wayzata Blvd, #200 Bloomington, MN 55305	16(0)
185	Milton Hom, OD	Kavita Surti, MD Maria Murillo Angela Zermeno Deborah Beltran Kristen Hipolito Melissa Quintana	Milton M. Hom, OD, FAAO 1131 E Alost Avenue Azusa, CA, 91702	31(18)
241	Randall Jacobson, MD	Alan Johnson, OD Thomas Riley, OD Kelly Moffatt, OD Jennifer Kerns, OD Shelia Wadhwa, OD Eileen Dittman, RN Dylan Waidelech, COA Brian Skea	Spokane Eye Clinical Research 427 South Bernard Street Spokane, WA 99204	7(1)
246	Yian Jin Jones, MD	Jason Jonathan Jones, MD Wing C. Hsieh, OD, FAAO Jacob A. Woldt, OD	Jones Eye Clinic 4405 Hamilton Boulevard Sioux City, IA, 51104	18(10)
205	Barry Katzman, MD	Nicole Kahel Pamela Emery	West Coast Eye Care Associates 6945 El Cajon Boulevard San Diego, CA, 92115	35(21)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
128	Kathleen Kelley, OD	Francis Price, MD Faye Peters, OD Clorissa Quillin Marianne Price Amanda Lopez	Price Vision Group 9002 North Meridian Street Suite #100 Indianapolis, IN 46260 Cornea Research Foundation of America 9002 North Meridian Street Suite 212 Indianapolis, IN 46260	35(32)
226	Charles Kirby, MD	Michael Yablick, MD	Chattanooga Eye Institute, P.C. 5715 Cornelison Road Building 6600 Chattanooga, TN, 37411	9(0)
194	Bruce Harvey Koffler, MD	Amber Barnes Merisa Stone	Koffler Vision Group 120 North Eagle Creek Drive Suite 431 Lexington, KY, 40509	11(6)
131	Michael Korenfeld, MD	Nathan M. Tuttle, OD Janet Renee Zeitzmann, RN Michelle M. Mueller	Comprehensive Eye Care, Ltd. 901 East 3 rd Street Washington, MO 63090	17(6)
186	John F. Kozlovsky, MD	Jeannine E. Camacho, OD Richard L. Delay, OD Patricia Martinez Alberto Molinar Gustavo Garcia Lizette Garcia-Casas Stephanie E. Camacho	Kozlovsky Delay & Winter Eye Consultants, LLC 2929 Mossrock, Suite 104 San Antonio, TX 78230	36(21)
227	Heath Lemley, MD	Mark D. Mayle, MD Lauren R. DiGiovine, MD	Regional Eye Associates 1255 Pineview Drive Morgantown, WV, 26505	14(4)
206	Jeffrey Raymond Lozier, MD	Karen Mossbarger, CRC Lynette Phifer, COA Ruth Bangs, Marisol Perez	Arch Health Partners 15611 Pomerado Road, 4 th Floor Poway, CA 92064	5(1)
248	Frank Wilson McDonald, MD	Jeffery Levenson, MD Curtis Schmidt, OD Vontrece Williams	Levenson Eye Associates 751 Oak Street, Suite 200 Jacksonville, FL 32204	14(2)
207	Jonathan Isaac Macy, MD	Shirin Yousefi, OD Scott A. Kaesemeyer Andrea Veneziano	Macy Eye Center 8635 West Third St. #360 W Los Angeles, CA, 90048	7(3)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
187	Parag Majmudar, MD	Maria Rosselson, MD Tiffany Andrzejewski, OD Charles Faron, OD	Chicago Cornea Consultants 1585 N. Barrington Rd, #502 Hoffman Estates, IL 60169	36(27)
111	Joseph Ruben Martel, MD	James B. Martel, MD Martha Orozco Cortes Nastya Padure Diana Petrashishin Unsa Anwar Liliya Shuprudko Olga Mikhaleenko	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670	64(31)
195	John C. Meyer, MD	Kellye Johnson Mandy Kessinger Angela Warfield Spencer Holley Guruprasad R. Pattar, MD, PhD	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	60(19)
208	Majid Moshirfar, MD	Steven Linn, OD Michele Avila, OD Jordan Desautels David Petersen Allison Kapp	Hoopes Vision 11820 South State St, #200 Draper, UT, 84020	4(0)
209	Jay Mulaney, MD	None	Central Florida Eye Associates 814 Griffin Road Lakeland, FL, 33805	5(3)
133	Kelly Kinney Nichols, OD, MPH, PhD, FAAO	Anna Ablamowicz, OD, FAAO Stephani Cox, OD, FAAO Jillian Meadows, OD, MS, FAAO Mansoor Saleh, MD	University of Alabama at Birmingham School of Optometry Henry Peters Building 1716 University Blvd. Birmingham, AL 35294	114(13)
188	Yen Dang Nieman, MD	Robert E. Marquis, MD Thomas R. Walters, MD Blythe E. Monheit, MD John W. Branch, MD Robert Stapper Jamie Jonson Krisi Lopez Elaine Marcin Tracey Knox Jody Redden Carol Stapper	Texan Eye, PA/Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731-4203	23(12)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
228	Thomas Lynn Nix, MD	James David Cullins, OD Ellen Lawrence, OD David Jenkins, LPN, CCRC Blake Davis, LPN, CRC	NEA Baptist Clinic Ophthalmology 4802 East Jonson Avenue Jonesboro, AR, 72401	2(0)
235	Matthew Oliva, MD	Heather Smith, CRC Stacey L. Hoins, OD Benjamin T. Taylor, OD John D. Welling, MD	Medical Eye Centar 1333 East Barnett Road Medford, OR, 97504	3(0)
154	Richard J. Ou, MD	John M. Lim, MD Caroline Beard, CRC Santa Montelongo, CRC Stephanie Verkin, CRC Gihan Romany, CRC Bhavna Shah, CRC Anne Marie O’Keeffee Erica Suarez Naina Sudarshan	Houston Eye Associates 915 Gessner Street, Suite 250 Houston, TX 77024	6(3)
189	Bernard R. Perez, MD	Don J. Perez-Ortiz, MD, FACS Michelle Whidden Gelissa Mann	International Research Center 4506 Wishart Place Tampa, FL 33603	80(14)
210	Henry D. Perry, MD	Surajit Saha, MD Alanna Sari Nattis, MD Raymond Mariani, OD	Ophthalmic Consultants of Long Island 2000 N. Village Ave. #402 Rockville Centre, NY, 11570	16(2)
197	Daniel Powell, OD, MS, PhD	David A. Berntsen, OD, PhD, FAAO Nicky Ray Holdeman Rachel Redfern, OD, PhD, FAAO Eric R. Ritchey, OD, PhD, FAAO Maria K. Walker	The Ocular Surface Institute (TOSI), University of Houston 505 J Davis Armistead Building Houston, TX, 77204	47(13)
130	Steven Howard Rauchman, MD	Robert J. Smyth Medina Joanne Perry Rocio Rodriguez Denise Nunez Rocio Garcia Elise Levine	North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	75(43)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
156	Harvey J. Reiser, MD	Carrie A. Cardillo, OD Patti J. Myers Christen Hogan Patty Yuhas	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704	16(7)
198	Jason S. Rothman, MD	Brett Bielory, MD Amanda Campbell Joanne Berry	Ophthalmic Consultants of Boston 50 Staniford Street, Suite 600 Boston, MA, 02114	5(1)
190	Mark Rubin, MD	Michelle Marie Wholly, COS Patrizia Rubin Jennifer Wilson	International Eye Associates PA 1545 Hand Avenue Suite B-3 Ormond Beach, FL, 32174	18(4)
118	Kenneth Sall, MD	Haily Ho, MD Julie Kim, OD Jade Davis, OD Leticia Guzman-Cisneros Cindy Lee Ilanie Marie Shiell Patricia Manjarrez	Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701	99(38)
119	John D. Sheppard, MD	Walter O. Whitley, OD Cecelia Koetting, OD	Virginia Eye Consultants 241 Corporate Blvd Norfolk, VA 23502	12(3)
157	Philip Lee Shettle, DO	None	Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	40(33)
158	Bruce E. Silverstein, MD	Christopher Lin, MD Robert G. Trent, MD Bryan G. Crum, MD Kathrine Owens Kelly Miller Sandra Kelly	Shasta Eye Medical Group, Inc. 3190 Churn Creek Road Redding, CA 96002 Shasta Eye Medical Group, Inc. 900 Butte Street Redding CA 96001	20(2)
234	Annette Chang Sims, MD	Richard Scott Hoffman, MD	Drs. Fine, Hoffman & Sims, LLC, 1550 Oak Street, #5 Eugene, OR, 97401	15(0)
191	Nancy Stephens, OD	William Lipsky, MD, FACS Teresa M. Solis Barbara N. Lund	InTouch Clinical Research Center, Inc. 11550 Fuqua Street Suites 215 & 250 Huston, TX, 77034	47(33)
192	Gregory Michael Sulkowski, MD	James D. Hurt, OD Ashley Griffith, BS Kimberly Martin, COA	Taustine Eye Center 1169 Eastern Pky, #3427&3334 Louisville, KY 40217	10(2)

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Site No.	Investigator Name	Sub-Investigator(s) Name	Address	Enrolled (Randomized)
121	Joseph Tauber, MD	Megan Hefter Greg Griffe	Tauber Eye Center 4400 Broadway Street, Suite 202 Kansas City, MO 64111	35(14)
123	Navin Tekwani, MD	Hiralal Tekwain, MD Lisa Dinsmore Ashley Duggan Lisa Schepp	Tekwani Vision Center 9911 Kennerly Road, Ste. A St. Louis, MO 63128	27(6)
212	Melissa Toyos, MD, FAAO, FACS	Ronaldo Toyos, MD Dustin Briscoe, OD Patricia Mathey Sara Gill	Toyos Clinic 2204 Crestmoor Road Nashville, TN, 37215	22(11)
213	Michael Tran, MD, FACS	None	Michael K Tran, M.D., Inc 15355 Brookhurst St., # 104 Westminster, CA, 92683	32(10)
214	Albert T. Chang, OD	Lawrence Wan, OD Julie Lee, OD	Family Eye Care Center 338 East Hamilton Avenue Campbell, CA, 95008	11(4)
124	Jeffrey Whitsett, MD	Jesse McKey, MD David Fu, OD	Whitsett Vision Group 1237 Campbell Road Houston, TX 77055	44(37)
125	Steven Wilson, OD	Howard Lazarus, MD Liana Davis, LPN Debra Paige Bunch Carren Deneen Jordan	John-Kenyon American Eye Institute 519 State Street New Albany, IN 47150	24(14)
215	David Louis Wirta, MD	Linda Wirta Yvette Abbasia Heather Tyner Kimberly Abbasia Mai Giang Jenny Porto Taylor Fogarty Shelby Buckley Nica Sabouni Haley Fritz William Kiely Tina Johns	Eye Research Foundation 520 Superior Avenue Suite 235 Newport Beach, CA, 92663	71(36)
224	Daniel V. Zimmer, MD, FACS	Natasha Hindman, OD Kimberly A. Spehar Marjorie Lopiccolo, CRC Adam M. Borowski Timothy C McKernan, OD	Scott & Christie and Associates, PC 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066	60(42)

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6.3.2. Study Results KPI-121-C-007

Compliance with Good Clinical Practices

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Financial Disclosure

See Appendix 13.2 of this review.

Patient Disposition KPI-121-C-007

	KPI-121 0.25% (N=452)	Vehicle (N=453)	Total (N=905)
Completed Study	447(98.9%)	448(98.9%)	895(98.9%)
Subjects Withdrawn Early from the Study	5(1.1%)	5(1.1%)	10(1.1%)
Reason for Study Exit			
Withdrawal by subject	2(0.4%)	2(0.4%)	4(0.4%)
Lost to follow-up	0	2(0.4%)	2(0.2%)
Other	3(0.7%)	1(0.2%)	4(0.4%)

ITT = intent to treat

Source: Table 14.1.2.1

A total of 2035 subjects were screened for the study; of these, 1126 were screening or randomization failures (i.e., subjects who failed to meet eligibility criteria at Visit 1 and/or at Visit 2) and 909 were screen successes and were randomized into the trial. Included in these 909 randomized subjects was 1 individual who enrolled in the study twice at 2 different sites and 2 individuals who completed the other phase 3 trial, KPI-121-C-006, and then enrolled in this trial. The second-participation data for these 3 individuals (Subject IDs (b) (6)) were not included in any analysis population. Thus, 906 subjects were eligible to be included in the analysis populations of the study. Of these, 1 subject (ID (b) (6)) did not receive treatment and was therefore also excluded from the ITT, safety, and PP populations.

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Protocol Violations/Deviations KPI-121-C-007

Deviation Type	KPI-121 0.25% (N=452)	Vehicle (N=453)
Study Product Deviation	162	151
Other	69	71
Study Visit Schedule Deviations	42	37
Missed Procedures	20	19
Inclusion & Exclusion Criteria	19	17
Qualification for Randomization	3	3
Concomitant Medication Deviation During Masked Period	1	4

ITT = intent to treat

Source: Table 14.1.7

Table 13 - Demographic Characteristics KPI-C-007

	KPI-121 0.25% (N=452)	Vehicle (N=453)	Total (N=905)
Age (yrs)			
Mean	59.1	59.3	59.2
SD	14.48	15.01	14.74
Median	61.5	62.0	62.0
Min, Max	19, 91	18, 93	18, 93
Gender, n (%)			
Male	120(26.5%)	99(21.9%)	219(24.2%)
Female	332(73.5%)	354(78.1%)	686(75.8%)
Ethnicity, n (%)			
Hispanic/Latino	118(26.1%)	118(26.0%)	236(26.1%)
Not Hispanic/Latino	334(73.9%)	335(74.0%)	669(73.9%)
Race, n (%)			
American Indian/Alaskan Native	0	0	0
Asian	39(8.6%)	35(7.7%)	74(8.2%)
Black/African-American	58(12.8%)	54(11.9%)	112(12.4%)
Native Hawaiian/Other Pacific Islander	1(0.2%)	1(0.2%)	2(0.2%)
White	345(76.3%)	352(77.7%)	697(77.0%)
Unknown	0	0	0
Other Race	7(1.5%)	9(2.0%)	16(1.8%)
Mixed	2(0.4%)	2(0.4%)	4(0.4%)

ITT = intent to treat; Max = maximum value; Min = minimum value; SD = standard deviation

Source: Table 14.1.4

The 905 subjects in the ITT and safety populations were predominantly female (76%) and white (77%), with a mean (range) age of 59 (18 to 93) years. No meaningful differences were observed between the treatment groups in terms of demographic characteristics.

Efficacy Endpoints - Primary Endpoints KPI-121-C-007

Table 14 - Summary of Primary Efficacy Results KPI-121-C-007

Primary Endpoint (Population)	KPI-121 0.25% (N = 452)		Vehicle (N = 453)		Trt Diff p-value ^a
	Day 1	Change at Day 15	Day 1	Change at Day 15	
Primary ocular sign endpoint					
Conjunctival hyperemia scores ^b at Day 15 visit (ITT, mean [SD])	n = 452 2.0000 (0.62470)	n = 446 -0.3812 (0.60560)	n = 453 2.0397 (0.56694)	n = 447 -0.2371 (0.62256)	-0.16 < 0.0001
Primary ocular symptom endpoint					
ODS scores ^c at Day 15 (ITT; mean [SD])	n = 452 68.79 (15.459)	n = 445 -11.14 (19.901)	n = 453 68.70 (15.799)	n = 444 -9.24 (17.002)	-1.87 0.1298

ITT = intent to treat; ODS = ocular discomfort severity; SD = standard deviation; Trt Diff = between-group treatment difference (KPI-121 0.25% minus vehicle) using least square means

^a P-values were calculated based on an analysis of covariance with baseline value as covariate and treatment group and randomization strata as fixed effects.

^b Conjunctival hyperemia scores (using the CCLRU grading scale, from 0 [none] to 4 [severe]) were based on photographic assessment at a central masked reading center, in the worst region (as defined from evaluations of photographs at Day 1) of the study eye. The study eye was defined using an algorithm described in the statistical analysis plan.

^c ODS scores (from 0 to 100 mm) were derived from data entered into diaries by subjects. Scores were general evaluations across both eyes; there were not separate questions for each eye. Higher scores indicate more severe ocular discomfort. Three-day means were calculated using available data from the 3 days prior to Day 15 (regardless of when Visit 4 [ie, the Day 15 visit] occurred) and the 3 days prior to Day 1. Only available data are used without imputation; if the target number of prior days of diary data was not available, the number of days contributing to the average could be less than the target.

Source: Table 14.2.1.1, 14.2.1.3

Statistically significant results favoring KPI-121 0.25% over vehicle were observed for 1 of the 2 primary endpoints defined for this study. A statistically significant between-group difference was observed for the primary efficacy endpoint of change from baseline in bulbar conjunctival hyperemia scores in the worst region of the study eye (determined based on Day 1 photographs) at the Day 15 visit, based on masked photographic assessment conducted at a central photographic reading center. The between-group difference was -0.16 favoring KPI-121 0.25% over vehicle ($p < 0.01$).

For the primary efficacy endpoint of change in ODS scores from Day 1 to Day 15 using 3-day means, the between-group difference was -1.87 mm, favoring KPI-121 0.25% over vehicle, but not achieving statistical significance ($p = 0.13$).

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The applicant seeks approval of EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% dosed four times daily (QID) for the temporary relief of the signs and symptoms of dry eye disease. The applicant has conducted one Phase 2 study (Trial KPI-121-C-002) and two Phase 3 studies (Trial KPI-121-C-006 and -007) to support the efficacy and safety of the drug product for this indication.

Each of the 3 studies demonstrated superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary sign endpoint at Day 15.

Only Trial KPI-121-C-006 demonstrated superiority of the loteprednol etabonate ophthalmic suspension, 0.25% to the vehicle for the primary symptom endpoints. Trial KPI-121-C-002 and Trial KPI-121-C-007 failed to demonstrate superiority of loteprednol etabonate ophthalmic suspension, 0.25% for their primary symptom endpoint, although they both showed numerically favorable results.

In order to support an indication of the signs and symptoms of dry eye disease, an additional trial is recommended demonstrating replication of the sign and symptom results from KPI-121-C-006.

8. Review of Safety

8.1. Safety Review Approach

The primary evidence of safety reported within this new drug application to support EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is based on integrated data for the safety populations from 3 multicenter, double-masked, randomized, vehicle-controlled dry eye trials (Trials -002, -006, and -007). All 3 trials included KPI-121 0.25% QID and vehicle QID. Trial -002 included a 28-day treatment period, and Trials -006 and -007 included 14-day treatment periods. In all trials, the same formulations of KPI-121 0.25% and vehicle were used.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

For Trial -002, the treatment period was 28 days and the median duration of exposure to study treatment was 29 days for both treatment groups. For Trials -006 and -007, the treatment periods were 14 days and the median duration of exposure was 15 days for both treatment groups in both trials.

Table 15 - Exposure to Study Treatment (Trials -002, -006, -007)

		Trial KPI-121-C-002 28-day Treatment Period (ITT Population)		Trial KPI-121-C-006 14-day Treatment Period (Safety Population)		Trial KPI-121-C-007 14-day Treatment Period (Safety Population)	
		KPI-121 0.25% QID (N = 73)	Vehicle QID (N = 77)	KPI-121 0.25% QID (N = 459)	Vehicle QID (N = 456)	KPI-121 0.25% QID (N = 452)	Vehicle QID (N = 453)
Exposure (days)	n	73	77	459	456	452	453
	Mean	28.6	28.6	14.8	14.8	14.8	14.6
	SD	1.49	1.59	1.60	1.67	3.80	1.54
	Median	29.0	29.0	15.0	15.0	15.0	15.0
	Min, Max	20, 35	20, 33	1, 22	8, 25	3, 86	7, 25
1 to 5 days	n (%)	0	0	2 (0.4)	0	3 (0.7)	0
6 to 10 days	n (%)	0	0	1 (0.2)	4 (0.9)	3 (0.7)	5 (1.1)
11 to 17 days	n (%)	0	0	443 (96.5)	432 (94.7)	431 (95.4)	436 (96.2)
> 17 days	n (%)			13 (2.8)	20 (4.4)	15 (3.3)	12 (2.6)
18 to 25 days	n (%)	1 (1.4)	1 (1.3)				
> 25 days	n (%)	72 (98.6)	76 (98.7)				

ITT = intent to treat; Max = maximum; Min = minimum; QID = four times daily; SD = standard deviation

Note: Trial KPI-121-C-002 calculated exposure based on the ITT population, per the statistical analysis plan. The safety population differed from ITT by 1 subject who received a different treatment than they were randomized to receive. There were 72 and 78 subjects, respectively, in the KPI-121 0.25% and vehicle groups in the safety population of Trial KPI-121-C-002.

Source: Module 5.3.5.1, CSR KPI-121-C-002, [Table 14.1.6](#); CSR KPI-121-C-006, [Table 14.3.7](#); CSR KPI-121-C-007, [Table 14.3.7](#)

Source: Module 2.7.4

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

Adverse events were categorized as ophthalmic and systemic. Analyses were prepared using an integrated safety population for the 3 trials, which was defined as all randomized subjects who received at least 1 dose of study treatment and from whom at least 1 safety assessment was obtained after randomization.

Treatment-emergent adverse events (TEAEs) were defined as those events with onset after the first dose of randomized study treatment or, if occurring prior to first dose, worsened after administration of first dose.

8.3.3. Routine Clinical Tests

Routine ophthalmic examination assessments were conducted on all subjects including visual acuity assessments, slit lamp examination, and dilated fundus examinations in Trials -002, -006, and KPI-121-C-007. Urinalysis, hematology, and serum chemistry were conducted in Trial KPI-121-C-009; vital signs were monitored in Trial KPI-121-C-009.

8.4. Safety Results

8.4.1. Deaths

No deaths have been reported in any clinical trial of EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%.

8.4.2. Serious Adverse Events

Table 16 - Treatment-Emergent Serious Adverse Events (Integrated Safety Population, Trials KPI-121-C-002, KPI-121-C-006, and KPI-121-C-007)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 983)	Vehicle QID (N = 987)
Number (%) of Subjects Reporting Any Serious AE	4 (0.4)	0
Gastrointestinal Disorders	1 (0.1)	0
Diverticulum intestinal	1 (0.1)	0
Hepatobiliary Disorders	1 (0.1)	0
Cholelithiasis	1 (0.1)	0
Injury, Poisoning and Procedural Complications	1 (0.1)	0
Hip Fracture	1 (0.1)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.1)	0
Intervertebral Disc Protrusion	1 (0.1)	0

AE = adverse event; QID = four times daily

Note: At each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

Source: Module 5.3.5.3, [ISS Table 3.5](#)

Serious adverse events reported for the studies were consistent with the patient population:

- Subject (b) (6) (002) reported cholelithiasis on Day 29, severe in intensity. It resolved without sequelae within 24 hours of onset and resulted in the subject's discontinuation from the study.
- Subject (b) (6) (007) reported "diverticulum intestinal" on Day 3, which was moderate in severity. It resolved on Day 6 following treatment with a concomitant medication.
- Subject (b) (6) (007) reported hip fracture on Day 4, which was severe. It resolved on Day 15 following surgical repair and resulted in the subject's discontinuation from treatment.
- Subject (b) (6) (007) reported intervertebral disc protrusion on Day 11, which was severe. It resolved on Day 23 following treatment with concomitant medication.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the 3 dry eye trials, 1970 subjects were enrolled, received at least 1 dose of study treatment, and were included in the safety populations. Of these, 983 subjects were treated with KPI-121 0.25% QID and 987 subjects were treated with vehicle QID. The majority ($\geq 99.0\%$) of subjects completed the trial according to the respective protocol. Nineteen subjects (1.0%; 19/1970) discontinued the trials early, primarily due to withdrawal by subject or other reason.

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In Trial KPI-121-C-002, one subject in the KPI-121 0.25% group discontinued from the trial due to an AE (cholelithiasis). The event was reported on Day 29 and was severe in intensity. It resolved without sequelae within 24 hours of onset.

Table 17 - Subject Disposition for Trials of Dry Eye Disease (Integrated Safety Population)

	KPI-121 0.25% QID (N = 983)	Vehicle QID (N = 987)	Overall (N = 1970)
Completed Trial	972 (98.9%)	979 (99.2%)	1951 (99.0%)
Subjects Withdrawn Early from the Trial	11 (1.1%)	8 (0.8%)	19 (1.0%)
Reason for Early Withdrawal			
Withdrawal by subject	5 (0.5%)	3 (0.3%)	8 (0.4%)
Adverse event	1 (0.1%)	0	1 (0.1%)
Lost to follow-up	1 (0.1%)	1 (0.1%)	2 (0.1%)
Physician decision	0	0	0
Pregnancy	0	0	0
Other	4 (0.4%)	4 (0.4%)	8 (0.4%)

QID = four times daily

Source: Module 5.3.5.3, [ISS Table 1.1.1](#)

In the 3 dry eye trials, treatment-emergent AEs leading to permanent withdrawal of study treatment were reported in 0.5% (5/983) and 0.4% (4/987) of subjects in the KPI-121 0.25% QID and vehicle QID groups, respectively. The AEs leading to permanent withdrawal of subjects in the KPI-121 0.25% QID group were conjunctival hyperemia, conjunctival edema, eye pruritus, cholelithiasis, drug hypersensitivity, hip fracture, and dyspnea (1 subject each). AEs leading to permanent withdrawal in the vehicle QID group were corneal infiltrates, eye irritation, vision blurred, herpes zoster, nasopharyngitis, and nausea (1 subject each).

Table 18 - Number (%) of Subjects Reporting Adverse Events Leading to Permanent Withdrawal of Study Treatment (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 983)	Vehicle QID (N = 987)
Number (%) of Subjects Reporting Any AE Leading to Permanent Withdrawal of Study Treatment	5 (0.5)	4 (0.4)
Eye Disorders	1 (0.1)	2 (0.2)
Conjunctival Hyperaemia	1 (0.1)	0
Conjunctival Oedema	1 (0.1)	0
Corneal Infiltrates	0	1 (0.1)
Eye Irritation	0	1 (0.1)
Eye Pruritus	1 (0.1)	0
Vision Blurred	0	1 (0.1)
Infections and Infestations	0	2 (0.2)
Herpes Zoster	0	1 (0.1)
Nasopharyngitis	0	1 (0.1)
Gastrointestinal Disorders	0	1 (0.1)
Nausea	0	1 (0.1)
Hepatobiliary Disorders	1 (0.1)	0
Cholelithiasis	1 (0.1)	0
Immune System Disorders	1 (0.1)	0
Drug Hypersensitivity	1 (0.1)	0
Injury, Poisoning and Procedural Complications	1 (0.1)	0
Hip Fracture	1 (0.1)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1)	0
Dyspnoea	1 (0.1)	0

AE = adverse event; QID = four times daily

Note: At each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

Source: Module 5.3.5.3, [ISS Table 3.6](#).

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

AEs were reported by 15% (143/983) and 13% (123/987) of subjects in the KPI-121 0.25% QID and vehicle QID groups, respectively. The most frequently reported preferred term was instillation site pain, which was reported by 6% of subjects in the KPI-121 0.25% QID group and 6% of subjects in the vehicle QID group. All other AEs were reported by $\leq 1\%$ of subjects in the KPI-121 0.25% QID group.

Table 19 - Number (%) of Subjects Reporting Common ($\geq 1\%$ in Either Treatment Group) Adverse Events (Integrated Safety Population)

System Organ Class Preferred Term	KPI-121 0.25% QID (N = 983)	Vehicle QID (N = 987)
Number (%) of Subjects Reporting Any AE ^a	143 (14.5)	123 (12.5)
General Disorders and Administration Site Conditions ^a	67 (6.8)	62 (6.3)
Instillation Site Pain	61 (6.2)	56 (5.7)
Eye Disorders ^a	40 (4.1)	50 (5.1)
Eye Irritation	8 (0.8)	12 (1.2)

AE = adverse event; PT = preferred term; QID = four times daily; SOC = system organ class

^a The numbers and percentages for overall AEs and AEs by SOC are inclusive of all PTs. PTs are only included in the table if $\geq 1\%$ of subjects in either treatment group reported that AE.

Note: at each level of summarization, subjects reporting more than one AE are only counted once. AEs coded using MedDRA Version 19.

Source: Module 5.3.5.3, ISS Table 3.2.1

8.4.5. Laboratory Findings

Urinalysis, hematology, and serum chemistry were conducted in Trial KPI-121-C-009, a single-center, open-label trial designed to evaluate the systemic pharmacokinetics and safety of KPI-121 0.25% QID in healthy adult subjects. No significant effects were noted.

8.4.6. Vital Signs

Vital signs were monitored in Trial KPI-121-C-009, a single-center, open-label trial designed to evaluate the systemic pharmacokinetics and safety of KPI-121 0.25% QID in healthy adult subjects. There was no significant effect.

8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were conducted in Trial KPI-121-C-009, a single-center, open-label trial designed to evaluate the systemic pharmacokinetics and safety of KPI-121 0.25% QID in healthy adult subjects. The electrocardiograms revealed no significant effect.

8.4.8. QT

QT studies were not performed during the clinical development of loteprednol etabonate ophthalmic suspension, 0.25%.

8.5. Safety Analyses by Demographic Subgroups

Pooled subgroup analyses were performed for all AEs by age group (< 65 and ≥ 65 years) and gender (male and female). There was no trend in the ISS data to indicate any difference in the safety profile of KPI-121 0.25% for the subgroups defined by age or gender.

8.6. Specific Safety Studies/Clinical Trials

The applicant did not perform assessment of corneal endothelial cell counts. The adverse event profile of loteprednol etabonate ophthalmic suspension is well-known. This is acceptable.

8.7. Additional Safety Explorations

8.7.1. Human Reproduction and Pregnancy

There are no adequate and well controlled studies with loteprednol etabonate in pregnant women.

8.7.2. Pediatrics and Assessment of Effects on Growth

This application was presented at the Pediatric Review Committee on March 13, 2019, with the proposed Indication of temporary relief of the signs and symptoms of dry eye disease. This application triggers PREA as a new indication. The applicant requested full waiver for pediatrics birth to less than 17 years of age because studies are impossible or highly impracticable. The PeRC agrees with the request for full waiver as presented in the Agreed iPSP.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

At the time of this submission, EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% has not been marketed in any region globally. Therefore, no postmarketing data are available on this specific product.

8.8.2. Expectations on Safety in the Postmarket Setting

This application is not recommended for approval. There are no recommended Post-marketing Requirements or Phase 4 Commitments.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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Formal labeling review and negotiation is deferred until additional data is submitted to support the proposed indication.

10.2. Nonprescription Drug Labeling
Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

This application is not recommended for approval. No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

This application is not recommended for approval. There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): KPI-121-C-002, -006, and -007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>140</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

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influenced by the outcome of the study: 0		
Significant payments of other sorts: 0		
Proprietary interest in the product tested held by investigator: <u>1</u>		
Significant equity interest held by investigator 0		
Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>140</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

(b) (6)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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