CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210933Orig1s000

SUMMARY REVIEW

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

Date	Ocotber 26, 2020
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	April 30, 2020
PDUFA Goal Date	October 30, 2020
Proprietary Name	EYSUVIS
Established Name	loteprednol etabonate ophthalmic suspension, 0.25%
Dosage Form	ophthalmic suspension
Indication	indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease
Dosing Regimen	Instill one to two drops of EYSUVIS into each eye four times daily for up to two weeks
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Dheera Semidey
Medical Officer Review	William Boyd
Statistical Review	Yunfan Deng
Pharmacology Toxicology Review	Andrew McDougal
OPQ Review Lead DP DS DMF Facility Reviewer Biopharm Micro	Chunchun N. Zhang Chunchun N. Zhang Sharon Kelly Feiyan Jin Akm Khairuzzaman Pike Andrew
CDTL Review	William M. Boyd
OSE/DMEPA	Nasim Roosta
OPDP	Carrie Newcomer
DMPP	Kelly Jackson

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
OPDP=Office of Prescription Drug Promotion
DMPP=Division of Medical Policy Programs

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%.

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.

Studies -002, -006, -007 and -011 demonstrated superiority of EYSUVIUS 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.

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 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.
Benefit	• 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.
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 two weeks 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 conjunctivitides 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.

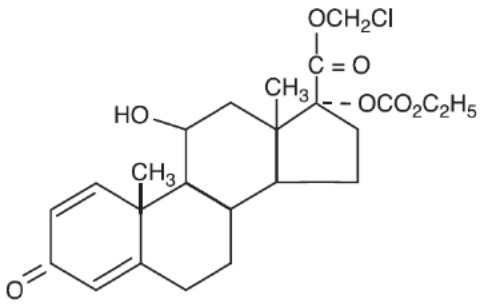
3. Patient Experience Data

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
	■ 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.	

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:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

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

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		
Loteprednol Etabonate related impurities[1] A. Loteprednol Etabonate related substances and impurities B. Total of all related impurities		
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.

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.
			• History of NAI inspections.	• Acceptable based on inspectional history review.

(b) (4)	• 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 10/26/2019:

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

In the original new drug application submission, the applicant had 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 endpoint. 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.

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.

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

Table 4 - 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 ≥ 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 ≥ 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 ≥ 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.
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 5 - 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.

	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 ($p = 0.03$).

	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.

Summary Efficacy Statement
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.

9. Safety

From the Clinical review dated 10/26/20:

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.

Overall Exposure

For the 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 6 - 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) (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

Serious Adverse Events

Table 7 - 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.

Treatment Emergent Adverse Events
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 ≤ 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 8 - Number (%) of Subjects Reporting Common (≥ 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 ≥ 1% of subjects in either treatment group reported that AE.
Source: Module 5.3.5.3, ISS Table 3.2.1

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

Summary Safety Statement
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 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.

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 agreed with the request for full waiver as presented in the Agreed iPSP.

12. Other Relevant Regulatory Issues

BIOSTATISTICS
From the Biostatistics review dated 8/15/20:

The three studies -002, -006, and -007 demonstrated a consistent treatment effect of LE 0.25% versus vehicle in terms of dry eye sign – conjunctival hyperemia (at Day 29 for Study 002, and at Day 15 for Studies 006 and -007); however, the three studies showed less consistent results for the dry eye symptom – change from baseline in ocular discomfort scores (ODS) at Day 15 using the 3-day mean. A complete response letter was sent to the applicant on 08/07/2019, the Division 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.

Table 1 lists the primary sign and symptom endpoints for the four studies. Conjunctival hyperemia scores were 5-level scales from 0 (none) to 4 (severe); corneal staining scores were 4- level scales from 0 (none) to 3 (severe); and ocular discomfort scores (ODS) was a visual analog scale from 0 to 100 mm, where 0 indicated “very mild” and 100 indicated “very severe.”

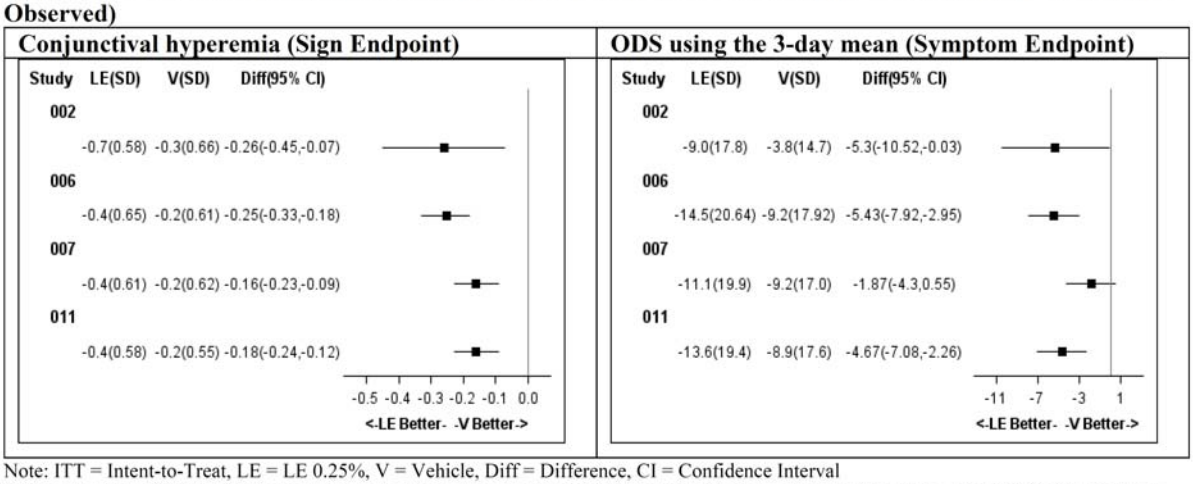
Table 1: Summary of Primary Efficacy Endpoints

	Study 002	Study 006	Study 007	Study 011
Sign	Mean conjunctival hyperemia scores in the worst region of the study eye at Day 29	Change from baseline in conjunctival hyperemia scores in the worst region of the study eye at Day 15 Change from baseline in inferior corneal staining scores in the study eye at Day 15	Change from baseline in conjunctival hyperemia scores in the worst region of the study eye at Day 15	As the first secondary endpoint: Change from baseline in conjunctival hyperemia scores in the worst region of the study eye at Day 15
Symptom	Mean ODS at Day 29 using the 7-day mean	Change from baseline in ODS at Day 15 using the 3-day mean Change from baseline in ODS at Day 15 using the 3-day mean in subgroup of patients with ODS ≥ 68 mm one day prior to Day 1	Change from baseline in ODS at Day 15 using the 3-day mean	Change from baseline in ODS at Day 15 using the 3-day mean Change from baseline in ODS at Day 15 using the 3-day mean in subgroup of patients with ODS ≥ 68 mm one day prior to Day 1

Source: Table 1 of Summary of Clinical Efficacy.

All four 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 demonstrated superiority of the LE 0.25% to the vehicle for its own primary sign endpoint at Day 29 and for the Phase 3 studies' primary sign endpoint at Day 15. As presented in Figure 1, two studies (006 and 011) demonstrated superiority of the LE 0.25% to the vehicle for the primary symptom endpoint of change from baseline in ODS at Day 15. However, the other two studies (002 and 007) failed to demonstrate superiority of LE 0.25% for their pre-defined primary symptom endpoint but both showed nominal difference favoring the LE group.

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



Note: ITT = Intent-to-Treat, LE = LE 0.25%, V = Vehicle, Diff = Difference, CI = Confidence Interval
* The estimated difference (95% CI and p-value) was based on an ANCOVA model with treatment, baseline values, and stratification variables.

Source: Table 11 of Study 006 CSR, Table 11 of Study 007 CSR, and Table 11 of Study 011 CSR.

Based on the collective evidence of all four studies, there were treatment effects of LE 0.25% versus vehicle in terms of reducing conjunctival hyperemia (dry eye sign) and lowering ocular discomfort score (dry eye symptom).

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 8/21/2020. DMEPA completed a labeling review on 8/17/20.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)
The Office of Prescription Drug Promotion (OPDP) completed a review of the substantially complete labeling on 9/23/20, and the patient labeling on 10/13/2020. The patient labeling was subsequently withdrawn by the applicant.

DIVISION OF MEDICAL POLICY PROGRAMS (DMPP)
The Division of Medical Policy Programs (DMPP), in conjunction with OPDP, completed a review of the patient labeling on 10/13/2020.

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 KPI-121-C-011

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 82 principle investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: 0 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) 82 principal investigators		
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). The Division did not request additional OSI inspections for study KPI-121-C-011.

13. Regulatory Action

NDA 210933 EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% will be approved for the for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease. There are no recommended post marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post marketing collection and reporting of adverse experiences associated with the use of the drug product.

14. Labeling

The agreed-upon labeling for NDA 210933 EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25% is included below.

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 01:56:23 PM

WILEY A CHAMBERS
10/26/2020 04:07:08 PM