CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210565Orig1s000

SUMMARY REVIEW

Deputy Division Director and Cross-Discipline Team Leader Review
NDA 210565

Date	August 22, 2018
From	Wiley A. Chambers, M.D., and William M. Boyd, M.D.
Subject	Deputy Division Director and Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	210565
Applicant	Kala Pharmaceuticals, Inc.
Date of Submission	October 24, 2017
PDUFA Goal Date	August 24, 2018
Proprietary Name	Inveltys
Established or Proper Name	Loteprednol etabonate ophthalmic suspension, 1%
Dosage Form(s)	Topical ophthalmic (b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of post-operative inflammation and pain following ocular surgery
Applicant Proposed Dosing Regimen(s)	Instill one to two drops into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period
Regulatory Action	Approval

1. Benefit-Risk Assessment

Inveltys (loteprednol etabonate ophthalmic suspension) 1%, also referred to as KPI-121 within this review, will be approved for the treatment of post-operative pain and inflammation following ocular surgery.

The results from the clinical development program for KPI-121 ophthalmic suspension 1%, administered as 1 to 2 drops to the affected eye twice daily for 2 weeks following surgery, is safe and effective for the treatment of post-operative inflammation and pain following ocular surgery. A risk management plan is not necessary given the known risks of this class of products (such as cataract formation and the increase in Intraocular Pressure (IOP)).

Studies KPI-121-C-001 and KPI-121-C-00 demonstrated that in patients who underwent cataract surgery, a significantly higher percentage of patients had 1) complete resolution (grade = 0) of anterior chamber cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 and 2) complete resolution (grade = 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15.

The most commonly reported ocular adverse reactions occurring in Inveltys (loteprednol etabonate ophthalmic suspension) 1% treated subjects were eye pain (1%) and posterior capsular opacification (1%).

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
The data contained in this submission establishes the efficacy of Inveltys (loteprednol etabonate ophthalmic suspension) 1% by demonstrating that in patients who underwent cataract surgery, a higher percentage of patients had 1) complete resolution (grade = 0) of anterior chamber cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 and 2) complete resolution (grade = 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15. The most commonly reported adverse reactions occurring in Inveltys (loteprednol etabonate ophthalmic suspension) 1% subjects were eye pain (1%) and posterior capsular opacification (1%). The potential benefits of Inveltys (loteprednol etabonate ophthalmic suspension) 1% through reduction of postoperative inflammation and postoperative pain outweigh the identified risks as demonstrated in the clinical studies submitted with this NDA application.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Inflammation, including postoperative inflammation, can lead to permanent damage to the anterior and posterior segments of the eye and to elevations of intraocular pressure which can damage the optic nerve.	Postoperative inflammation can be controlled and managed with the use of nonsteroidal or steroid products in the postoperative setting.
Current Treatment Options	• Currently available treatments for postoperative inflammation following ocular surgery include the use of steroidal or nonsteroidal anti-inflammatory drug products.	This product would provide an alternative steroid preparation, administered topically twice daily to the eye.
Benefit	• Reduction, specifically clearance, of inflammation, in the form of anterior chamber cells is a benefit; anterior chamber cells can be monitored by direct visualization of the anterior changer of the eye.	Inveltys (loteprednol etabonate ophthalmic suspension) 1% was superior to its vehicle in clearing the signs of postoperative inflammation and reducing of postoperative pain.
Risk and Risk Management	• Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Use of steroids is also associated with increased risk of posterior subcapsular cataract formation. Prolonged topical use may also suppress the host immune response and increase the hazard of secondary ocular infections.	Loteprednol is expected to have the same potential adverse event profile as other corticosteroids. Routine postoperative monitoring is expected to identify these adverse events if they were to occur.

2. Background

Kala Pharmaceuticals is relying on the FDA's findings of safety and effectiveness for the approved listed drug NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% to support this 505(b)(2) application.

Loteprednol etabonate has been approved and on the US market for 20 years. Loteprednol etabonate was first approved in 1998, as Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%.

Loteprednol Etabonate Approved Products

NDA	Drug Tradename	Formulation	Indication
20503	Loteprednol etabonate ophthalmic suspension, 0.5% (Lotemax)	Suspension	Post-operative inflammation following (b) (4) surgery
200738	Loteprednol etabonate ophthalmic ointment, 0.5% (Lotemax)	Ointment	Post-operative inflammation and pain following (b) (4) surgery
202872	Loteprednol etabonate ophthalmic gel, 0.5% (Lotemax)	Gel	Post-operative inflammation and pain following (b) (4) surgery
50804	Loteprednol etabonate and tobramycin ophthalmic suspension, 0.5%/0.3% (Zylet)	Suspension	For steroid- responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or risk of bacterial ocular infection exists
20803	Loteprednol etabonate ophthalmic suspension, 0.2% (Alrex)	Suspension	Temporary relief of signs and symptoms of seasonal allergic conjunctivitis

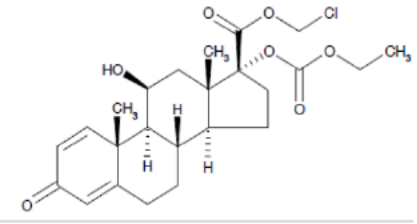
The following meetings/correspondence was held with the applicant during the course of their drug's development process under IND 117192:

- April 4, 2013 – Type B PIND (Pre-IND) meeting was held to discuss CMC, nonclinical and clinical questions.
- June 15, 2015 – Type C meeting was held to discuss product manufacturing, clinical development plans and given the known history of ophthalmic use of loteprednol it was agreed the measurement of endothelial cell counts would be not required.
- May 5, 2017 – Type B meeting was held to agree upon the clinical and non-clinical components of the planned NDA submission.

3. Product Quality

From the original Office of Product Quality Review dated 7/24/2018:

Chemical Name and Structure:
(11β, 17α) – 17 - [(Ethoxycarbonyl)oxy] – 11 – hydroxyl – 3 – oxoandrosta - 1,4 – diene –17 - carboxylic acid chloromethyl ester



The drug product is provided in a 5 mL LDPE [(b) (4)] with 2.8 mL fill for the commercial supply and 1.2 mL fill for the physician samples. Each [(b) (4)] is packaged in an individual carton with black/white printed package insert.

The drug substance manufacturer, [(b) (4)] has a drug master file (DMF) for loteprednol etabonate on file at the FDA. The release specifications for loteprednol etabonate from [(b) (4)]

Description and Composition of the Drug Product

Composition of Inveltys 1%

Ingredient	Quality Standard	Function	Amount (mg) in each mL of KPI-121 1%	Concentration (%w/v) in KPI-121 1%
Loteprednol etabonate	[(b) (4)]	Active Pharmaceutical Ingredient	10	1.0
Glycerin	USP-NF	[(b) (4)]		
Sodium citrate, dihydrate	USP-NF			
Poloxamer 407	USP-NF			
Sodium chloride	USP-NF			
Edetate disodium, dihydrate	USP-NF			
Citric acid, [(b) (4)]	USP-NF			
Benzalkonium chloride	USP-NF	Preservative	[(b) (4)]	0.01
Water for injection	USP-NF	[(b) (4)]		

[(b) (4)]

[(b) (4)] USP-NF: United States Pharmacopeia - National Formulary

[(b) (4)]

Source: Module 3.2.P.1.

Release Specification of the Drug Product

Quality control specifications for release of KPI-121 1% commercial fill (trade) bottles are provided. These specifications were updated in July 2018.

Table 1: Quality control specifications for release of KPI-121 1% commercial fill bottles

Attribute and Test	Method Number	Acceptance Criteria
Appearance	(b) (4)	White dropper bottle (b) (4)
	Visual Observation	
pH	(b) (4)	(b) (4)
Osmolality		
Benzalkonium Chloride Assay		
Particle Size		
Minimum Fill Volume	USP<755>	2.8 mL
Identity Loteprednol Etabonate (LE)	(b) (4)	(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 3.2.P.5.

Drug Product Container Closure

(LDPE) plastic bottle with nominal capacity of 5 mL; a controlled-drop, linear low-density polyethylene (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.

Table 1: KPI-121 1% container closure components

Part	Description	Manufacturer	Sterilizer
Bottle	5 mL Multi-dose Bottle	(b) (4)	NA
Tip	(b) (4) LLDPE Tip		(b) (4)
Cap	Pink HDPE Cap		
Overcap	Tamper-evident Overcap		NA

NA: not applicable
Note: Tip/cap assemblies are constructed at (b) (4)
Source: Module 3.2.P.7.

Inspections

Following a review of the inspectional histories of the drug substance and drug product manufacturing and testing facilities, there are no outstanding concerns related to the demonstrated manufacturing and testing capabilities. The overall facility review recommendation is adequate for approval.

Summary of Drug Substance Facility Information:

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.

Summary of Drug Product Facility Information:

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 with lack of quality defect signals.
			• New dosage form for the facility. • History of NAI inspections.	• Acceptable based on PAI results by inspection performed in (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.

Recommendation and Conclusion on Approvability from OPQ

NDA 210565, as amended, has provided sufficient product quality information to assure the identity, strength, purity, and quality of the proposed drug product Inveltys (loteprednol etabonate ophthalmic suspension), 1%. All information requests and review issues have been addressed.

The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on 7/13/2018. NDA 210565 is recommended for approval from Product Quality perspective.

4. Nonclinical Pharmacology/Toxicology

The PK study KPI-121-C-008 conducted by Kala, reviewed and concurred by the FDA Clinical Pharmacology group (see Section 5 of this review) demonstrated no measurable drug level or metabolites at a 1ng/mL level of detectability. Section 12.3 Pharmacokinetics of the proposed labeling thus states that following "twice-daily unilateral topical ocular dosing of INVELTYS for 14 days, the plasma concentrations of loteprednol etabonate were below the limit of quantitation (1 ng/mL) at all timepoints." Since 1 ng/mL in humans is below the normal steroid physiologic level, the limit of quantitation is relevant. The referenced Lotemax suspension product (NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%) also has a PK study in the original application demonstrating the same no detectability.

As per 21 CFR 201.57(b)(9)(i)(B), the applicant was requested to change the proposed language of the Risk Summary to: "INVELTYS is not absorbed systemically following topical ophthalmic administration and maternal use is not expected to result in fetal exposure to the drug." As per 21 CFR 201.57(b)(9)(ii)(A)(1), the Risk Summary of the Lactation section was also revised to: "INVELTYS is not absorbed systemically by the mother following topical ophthalmic administration, and breastfeeding is not expected to result in exposure of the child to INVELTYS."

From the original Pharmacology/Toxicology review dated 7/19/2018:

The Applicant submitted a 28-day ocular toxicology study in rabbits (report # 8286658), testing the clinical dose (KPI-121 1%). From a nonclinical perspective, treatment was well-tolerated and the study establishes ocular safety and systemic safety.

5. Clinical Pharmacology

From the original Office of Clinical Pharmacology review dated 7/31/2018:

The focus of the Clinical Pharmacology review of this NDA was to assess the systemic PK of LE, and its metabolites, PJ-90, and PJ-91*. Study KPI-121-C-008 characterized the PK exposure of LE, PJ-90, and PJ-91 in 20 healthy adult subjects following topical ocular administration of 2 drops of Inveltys 1% BID for 15 days in a randomly assigned study eye. Based on the findings of PK Study KPI-121-C-008, the reviewer agrees with the Applicant's conclusion that LE, PJ-90, and PJ-91 were not quantifiable in plasma on Days 1, 8 (trough), and 15 following topical ocular dosing of 2 drops in one eye of Inveltys 1% BID for 15 days (only one dose was administered on Day 15 of the Study) in healthy adult subjects.

The Clinical Pharmacology team recommends approval of NDA 210565 for Inveltys [loteprednol etabonate ophthalmic suspension, 1%] at the proposed dosing regimen (i.e., Instill one to two drops into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period) for the treatment of post-operative inflammation and pain following ocular surgery.

***Note:**

(b) (4)

6. Clinical Microbiology

Not applicable. This product is not an anti-infective.

7. Clinical/Statistical- Efficacy

From the original Medical Officer review dated 8/3/2018:

Table of Studies/Clinical Trials

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase 3	KPI-121-C-001	Efficacy and Safety of KPI-121 compared to vehicle. - Difference in proportion of eyes with complete resolution of anterior chamber cells (grade = 0) at Day 8 maintained through Day 15 - Difference in proportion of eyes with complete resolution of ocular pain (grade = 0) at Day 8 maintained through Day 15	Phase 3, multi-center, randomized, double masked, parallel group study of 2 concentrations and dosing regimens of KPI-121 vs. vehicle	PI-121 0.25% QID KPI-121 1% BID Vehicle A QID Vehicle B BID	380 total 125 KPI 121 1% 129 KPI-121 0.25% 126 Vehicle	Male and female subjects age ≥18 years who had undergone routine cataract surgery	14 Days
Phase 3	KPI-121-C-005	Efficacy and Safety of KPI-121 compared to vehicle. Same as KPI-121-C-001	Same as KPI-121-C-001	KPI-121 1% BID Vehicle BID	520 total 261 KPI 121 1% 259 Vehicle	Same as KPI-121-C-001	14 days

The efficacy of Inveltys (loteprednol etabonate ophthalmic suspension, 1%) dosed BID for the proposed indication was based on the review of 2 randomized, double-masked, vehicle-controlled studies (Studies KPI-121-C-001 and -005) studies.

The two primary endpoints were tested sequentially in both studies to maintain an overall Type I error of 0.05.

KPI-121-C-001

Primary Efficacy Results (ITT Population)

Hierarchical Testing Order	KPI-121 0.25% QID (N=129)	KPI-121 1% BID (N=125)	Vehicle (N=126)	Between-Group Difference for % Responders[a] (95% CI)	p-value
Complete Resolution (Grade 0) of Anterior Chamber Cells, n (%)	48 (37.2)	39 (31.2)	19 (15.1)		
1) KPI-121 0.25% QID vs. Vehicle				22.1 (11.7, 32.6)	<0.0001
2) KPI-121 1% BID vs. Vehicle				16.1 (5.9, 26.4)	0.0024
Complete Resolution (Grade 0) of Pain, n (%)	73 (56.6)	67 (53.6)	43 (34.1)		
3) KPI-121 1% BID vs. Vehicle				19.5 (7.4, 31.5)	0.0019
4) KPI-121 0.25% QID vs. Vehicle				22.5 (10.6, 34.4)	0.0003

BID = twice daily; QID = four times daily

[a] KPI-121 minus vehicle

Note: Subjects with complete resolution (Grade 0) of anterior chamber cells or of ocular pain at Day 8 and Day 15 to Day 15) are counted as responders. P-values are based re tests, unadjusted, wherein the significance level was 0.05.

For study KPI-121-C-001, complete resolution (grade = 0) of anterior chamber cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 31% of subjects in the KPI-121 1% BID group (loteprednol etabonate ophthalmic suspension, 1%) compared with 15% of subjects in the pooled vehicle group (p = 0.0024).

Complete resolution (grade = 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 54% of subjects in the KPI-121 1% BID group compared with 34% of subjects in the pooled vehicle group (p = 0.0019).

A statistical comparison between the 2 active treatment groups was performed for the primary efficacy variables. The results of this analysis demonstrated no significant differences between the KPI-121 1% BID and the KPI-121 0.25% QID groups in the proportions of subjects with complete resolution of anterior chamber cells at Day 8 and maintained through Day 15 without rescue medication prior to Day 15 (p=0.3130) or in the proportion of subjects with complete resolution of ocular pain at Day 8 and maintained through Day 15 without rescue medication prior to Day 15 (p=0.6320).

KPI-121-C-005

Primary Efficacy Results for KPI-121 1% and Vehicle Groups

	KPI-121 1% BID (N=261)	Vehicle BID (N=259)	Between-Group Difference for % Responders[a] (95% CI)	p-value
Complete Resolution (Grade 0) of Anterior Chamber Cells at Day 8 and Maintained Through Day 15 with no Rescue Medication Prior to Day 15, n (%)	54 (20.7)	32 (12.4)	8.3 (2.0, 14.7)	0.0105
Complete Resolution (Grade 0) of Ocular Pain at Day 8 and Maintained Through Day 15 with no Rescue Medication Prior to Day 15, n (%)	149 (57.1)	96 (37.1)	20.0 (11.6, 28.4)	<0.0001

For study KPI-121-C-005 complete resolution (grade = 0) of anterior chamber cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 21% of subjects in the KPI-121 1% group, compared with 12% of subjects in the vehicle group ($p = 0.0105$).

Complete resolution (grade = 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 was demonstrated in 57% of subjects in the KPI-121 1% group compared with 37% of subjects in the vehicle group ($p < 0.0001$).

Efficacy Summary Statement

Both studies demonstrated superiority of LE to its vehicle for both primary endpoints (i.e., the proportion of the subjects with complete resolution (grade 0) of anterior chamber (AC) cells at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15 and in the proportion of the subjects with complete resolution (grade 0) of ocular pain at Day 8 and maintained through Day 15 with no rescue medication prior to Day 15).

8. Safety

The safety of Inveltys (loteprednol etabonate ophthalmic suspension, 1%) was based on the review of Studies KPI-121-C-001 and -005.

Number (%) of Subjects Reporting Common (≥ 1% in Either Treatment Group) Adverse Events (Integrated Safety Population Trials KPI-121-C-001 and KPI-121-C-005)

System Organ Class Preferred Term	KPI-121 1% BID (N = 386)	Vehicle BID (N = 325)
Number (%) of Subjects Reporting Any AE[a]	53 (13.7)	57 (17.5)
Eye Disorders[a]	26 (6.7)	38 (11.7)
Eye Pain	4 (1.0)	9 (2.8)
Posterior Capsule Opacification	4 (1.0)	4 (1.2)
Photophobia	2 (0.5)	6 (1.8)
Corneal Oedema	2 (0.5)	4 (1.2)
Nervous System Disorders[a]	7 (1.8)	8 (2.5)
Headache	6 (1.6)	6 (1.8)
Infections and Infestations[a]	12 (3.1)	3 (0.9)
Nasopharyngitis	4 (1.0)	1 (0.3)

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 >2% of subjects in any treatment group reported that AE.
Note: at each level of summarization, subjects reporting more than one event are only counted once. AEs coded using MedDRA Version 16.1. Only the integrated data from the KPI-121 1% BID and Vehicle BID groups are presented in-text; additional data are available in the source table.

The risk of adverse events was low with eye pain and posterior capsule opacification occurring at 1% and headache at 2% in the KPI-121 1% drug group.

Number (%) of Subjects Reporting Severe Adverse Events (Integrated Safety Population, Trials KPI-121-C-001 and KPI-121-C-005)

System Organ Class Preferred Term	KPI-121 1% BID (N = 386)	Vehicle BID (N = 325)
Number (%) of Subjects Reporting Any Severe AE	4 (1.0)	7 (2.2)
Eye disorders	2 (0.5)	4 (1.2)
Eye pain	2 (0.5)	1 (0.3)
Cystoid macular oedema	0	1 (0.3)
Eye inflammation	0	1 (0.3)
Photophobia	0	1 (0.3)
Nervous system disorders	0	1 (0.3)
Cerebrovascular accident	0	1 (0.3)
Infections and infestations	1 (0.3)	0
Pneumonia	1 (0.3)	0
Gastrointestinal disorders	0	2 (0.6)
Abdominal pain	0	1 (0.3)
Vomiting	0	1 (0.3)
Hepatobiliary disorders	1 (0.3)	1 (0.3)
Cholecystitis	1 (0.3)	0
Cholelithiasis	0	1 (0.3)

AEs were reported as severe for 1% (4/386) of subjects in the KPI-121 1% BID group and 2% (7/325) in the vehicle BID group.

Deaths

No deaths were reported during any trial of KPI-121.

Subject Disposition

Subject Disposition for Phase 3 Trials of Post-Operative Inflammation and Pain (Integrated Safety Population, Trials KPI-121-C-001 and KPI-121-C-005)

	KPI-121 1% BID (N = 386)	KPI-121 0.25% QID (N = 129)	Vehicle BID (N = 325)	Vehicle QID (N = 60)	Overall (N = 900)
Completed Trial	382 (99.0%)	127 (98.4%)	319 (98.2%)	59 (98.3%)	887 (98.6%)
Subjects Withdrawn Early from the Trial	4 (1.0%)	2 (1.6%)	6 (1.8%)	1 (1.7%)	13 (1.4%)
Reason for Early Withdrawal					
Withdrawal by subject	1 (0.3%)	2 (1.6%)	5 (1.5%)	0	8 (0.9%)
Adverse event[a]	1 (0.3%)	0	0	0	1 (0.1%)
Lost to follow-up	0	0	1 (0.3%)	0	1 (0.1%)
Physician decision	0	0	0	1 (1.7%)	1 (0.1%)
Pregnancy	0	0	0	0	0
Other	2 (0.5%)	0	0	0	2 (0.2%)

a The AE leading to withdrawal was eye pain.

The median duration of exposure to study treatment was 14 days for subjects in the drug 1% BID, vehicle BID, and vehicle QID groups, and 15 days for subjects in the drug 0.25% QID group.

Summary Statement

The results from the clinical development program for Inveltys (loteprednol etabonate ophthalmic suspension) 1%, administered as 1 to 2 drops to the affected eye twice daily for 2 weeks following surgery, is safe and effective for the treatment of post-operative inflammation and pain following ocular surgery.

The most commonly reported ocular adverse reactions occurring in Inveltys treated subjects were eye pain (1%) and posterior capsular opacification (1%).

9. Advisory Committee Meeting

There were no issues raised during the review of this application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

This application did not trigger PREA.

Safety and effectiveness in pediatric patients for this product have not been established.

(b) (4)

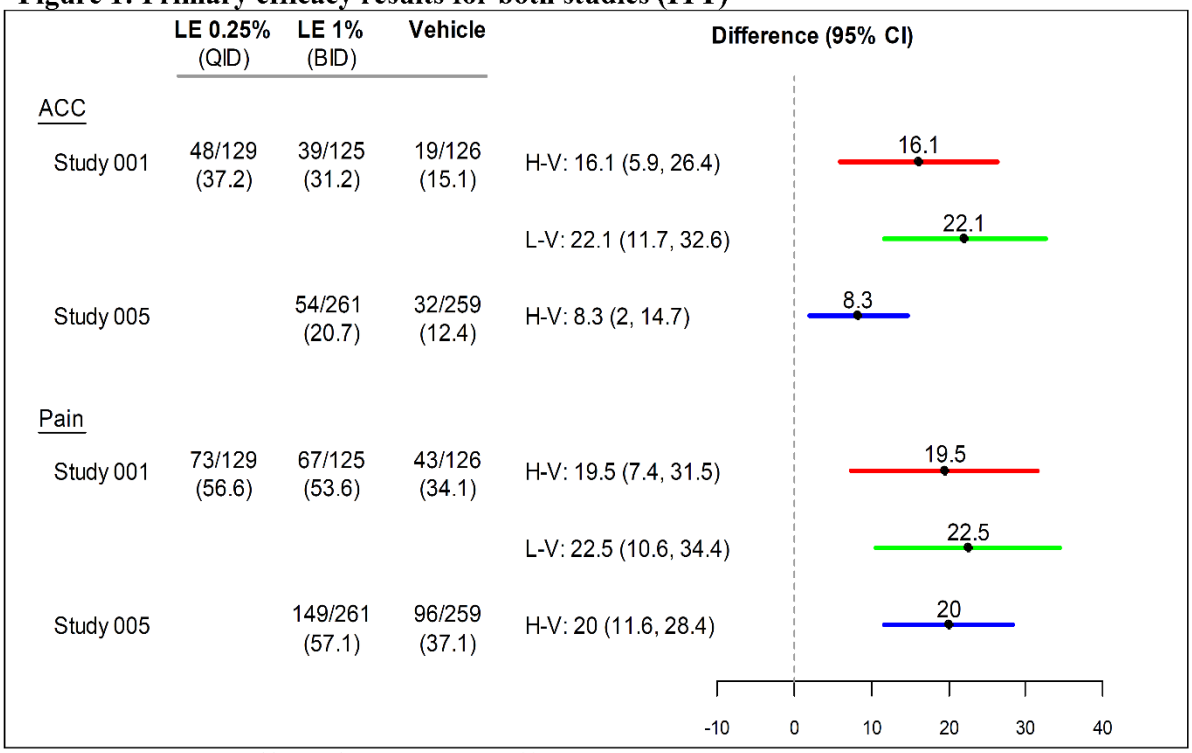
11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 6/14/2018:

This review focused on the two Phase 3, randomized, multicenter, double-masked, vehicle controlled studies (Studies 001 and 005) with similar designs. Study 001 randomized 380 subjects to receive either LE 0.25% four times a day (QID) (N = 129), LE 1% BID (N = 125), vehicle QID (N = 60), or vehicle BID (N = 66) for 2 weeks. Study 005 randomized 520 subjects to receive either LE 1% BID (N = 261) or the vehicle BID (N = 259) for 2 weeks.

The two primary endpoints were tested sequentially in both studies to maintain an overall Type I error of 0.05. In Study 001, the two vehicle groups were pooled for all efficacy analyses.

Figure 1: Primary efficacy results for both studies (ITT)



Source: KPI-121-001 CSR, Table 16 and KPI-121-005 CSR Table 15
Note: ITT = Intent-to-Treat population, which included all randomized subject. ACC = primary endpoint of AC cells. Pain = primary endpoint of ocular pain. H = LE 1% BID. L = LE 0.25% QID. Missing data was treated as failures.

Figure 1 above displays the efficacy results for the primary endpoints. Study 001 demonstrated superiority of both LE groups to the vehicle for both primary endpoints.

Study 005 also demonstrated superiority of LE 1% BID to the vehicle for both primary endpoints.

The significant primary results were supported by the analysis of the primary endpoints in the Per-Protocol population and by the analyses of majority of the non-primary endpoints.

DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Inveltys, and granted conditional acceptance on 1/26/2018. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA completed a formal review of the package insert and container labeling on 5/2/2018.

OPDP

The Office of Prescription Drug Promotion (OPDP) completed reviews of the package insert and carton and containers (8/9/2018) and had suggested revisions. These have been incorporated into the labeling with one exception: the placement of the image of the eye within the "V" of INVELTYS no longer

detracts, obfuscate, or de-emphasizes the established name of the product with the subsequent revision of the prominence of the proprietary name, as stated in 21 CFR 201.10(g)(2).

FINANCIAL DISCLOSURE
The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

(b) (6)

OSI
A routine Office of Scientific Investigations (OSI) audit was requested.

Per the OSI review dated 6/12//2018:

Inspections were requested for the following protocols in support of this application:

- **Protocol KPI-121-C-001**, "A Phase 3, Double-Masked, Randomized, Controlled Trial of KPI-121 in Postsurgical Inflammation"
- **Protocol KPI-121-C-005, "**A Phase 3, Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Efficacy of KPI-121 1% Ophthalmic Suspension in Subjects with Postsurgical Inflammation and Pain**"**

The clinical sites of Drs. Martel and Milstein were selected for inspection because of their relatively large enrollments and lack of previous inspections. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of the inspections of Drs. Martel and Milstein was No Action Indicated (NAI).

12. Labeling

NDA 210565 Inveltys (loteprednol etabonate ophthalmic suspension) 1% will be approved for the treatment of post-operative inflammation and pain following ocular surgery with the labeling attached as an Appendix in this review.

13. Regulatory Action

NDA 210565 Inveltys (loteprednol etabonate ophthalmic suspension) 1% will be approved for the treatment of post-operative inflammation and pain following ocular surgery. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
08/22/2018

WILEY A CHAMBERS
08/22/2018