

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**210933Orig1s000**

**NON-CLINICAL REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 210933

Supporting document/s: SD 1 (new NDA)

Applicant's letter date: October 15, 2018

CDER stamp date: October 15, 2018

Product: EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%

Indication: Temporary relief from the signs and symptoms of dry eye disease

Applicant: Kala Pharmaceuticals, Inc.

Review Division: Division of Transplant and Ophthalmology Products (DTOP), Office of Antimicrobial Products (OAP), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), HFD-590

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# 1 Executive Summary

## 1.1 Introduction

- The name of the Applicant is Kala Pharmaceuticals, Inc. (Kala Pharmaceuticals; Kala). On October 18, 2018, Kala submitted NDA 210933 in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetics Act for Eysuvis™ (loteprednol etabonate ophthalmic suspension) 0.25%, seeking approval for the indication of temporary relief of the signs and symptoms of dry eye disease.
- 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 020-583 (020583, 20583).
- The nonclinical Pharmacology/Toxicology (P/T) review identified no new safety concerns for Eysuvis™. P/T recommends approval of the NDA.
- The NDA file is available electronically via:  
<\\CDSESUB1\evsprod\NDA210933\210933.enx>

## 1.2 Brief Discussion of Nonclinical Findings

- Loteprednol etabonate (LE) is a corticosteroid ester initially approved in 1998 (Bausch & Lomb's NDA 20-583 for Lotemax®)<sup>1</sup>.
- KPI-121 (loteprednol etabonate ophthalmic suspension) was developed under Kala's IND 117192, to support both NDA 210565 for Inveltys™ and this NDA 210933 for Eysuvis™.
  - o Kala intended that the use of (b) (4) drug particles of loteprednol etabonate would result in enhanced penetration through the mucous layer of the tear film, compared to Lotemax®. The particle size profile is presented below (Table 3).
- The Applicant previously submitted NDA 210565 for Inveltys™ (loteprednol etabonate ophthalmic suspension) 1%, which was approved 8/22/2018. It was also submitted under the 505(b)(2) pathway, relying on the approved listed drug Lotemax® (NDA 20583).
  - o Inveltys™ is indicated for treatment of post-operative inflammation and pain following ocular surgery.
  - o The proposed indication for Eysuvis™ is temporary relief of the signs and symptoms of dry eye disease.
  - o Both NDA 210565 and this NDA 210993 have the same parent IND (IND 117192). The same rabbit toxicology study supports both products. The supporting pharmacokinetic (PK) studies largely overlap.

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<sup>1</sup> NDA 20583 original 1998 labeling accessed via:  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/1998/20583lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20583lbl.pdf) . Labeling has not been updated for NDA 20583.

- o Labeling<sup>2</sup> and a redacted version of the P/T review<sup>3</sup> for NDA 210565 are published.
  - o This review references NDA 210565's action package (Semidey, 8/24/2018, NDA 210565) and P/T reviews (McDougal; 7/19/2018, 8/01/2018; NDA 210565); these are archived in CDER's Document Archiving, Reporting and Regulatory Tracking System (DARRTS) database.
- P/T recommends dose margins for NDA 210933's labeling based on a rounded drop volume, for consistency across loteprednol etabonate labeling.
  - o For Inveltys™, the approved dosage and administration is one to two drops in the effected eye (i.e. single eye dosing) twice daily (BID) for two weeks (corresponding to 4 drops/person/day). The strength is 1% (10 µg/ul). The drop size is (b) (4). This corresponds to a total daily dose of (b) (4) µg/person/day.
  - o For Eysuvis™, the Applicant proposed a dosage and administration of one to two drops in each eye, four times a day (QID) for two weeks (corresponding to 16 drops/person/day). The strength is 0.25% (2.5 µg/ul). The drop size is (b) (4). This corresponds to a total daily dose of (b) (4) µg/person/day.
  - o From a P/T perspective, the difference between (b) (4) and (b) (4) is comparable, considering the labeled dosage and administration.
  - o For Eysuvis™, rounding the drop volume from (b) (4) to (b) (4) corresponds to a total daily dose of (b) (4) µg/person/day. This rounding approach avoids presenting slightly different numbers in the two labels.

## 1.3 Recommendations

### 1.3.1 Approvability

P/T recommends approval of NDA 210933. P/T has no recommendations for additional nonclinical studies.

### 1.3.2 Additional Non Clinical Recommendations

P/T requirements and recommendations have been fulfilled, for the clinical indication described in the original NDA 210933 submission. P/T has no recommendations for further testing.

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<sup>2</sup> NDA 210565 labeling dated 8/2018 accessed via:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210565s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210565s000lbl.pdf)

<sup>3</sup> P/T review for NDA 210565 by McDougal (7/19/2018 and 8/01/2018) accessed via:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/210565Orig1s000PharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210565Orig1s000PharmR.pdf)

### 1.3.3 Labeling

- For this NDA 210933, P/T proposes to align the nonclinical sections of Kala's labeling for loteprednol etabonate with NDA 202872 and NDA 208219.
  - This approach will create a discrepancy between Kala's labeling for this NDA 210933, and their labeling for NDA 210565.
- Bausch and Lomb has approved loteprednol etabonate labeling that complies with the Pregnancy and Lactation Labeling Rule (PLLR) for their NDA 202872/S002<sup>4</sup> and their NDA 208219<sup>5</sup>.
- Kala has previously approved loteprednol etabonate labeling for their NDA 210565.<sup>6</sup>
  - DTOP concluded that the nonclinical sections of labeling for NDA 210565 should be based on information available to the Applicant at the time of submission (10/24/2017).
  - Because Kala submitted NDA 210565 prior to approval of Bausch and Lomb's PLLR language, Sections 8.1, 8.2, and 13.1 have no new information, and are objectively less useful to readers compared to those sections as appearing in other published loteprednol etabonate labeling.

| Applicant's proposed text                                                                                              | P/T's recommendations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>8.1 Pregnancy</b><br><br>Risk Summary<br><div style="background-color: #cccccc; height: 100px; width: 100%;"></div> | <b>8.1 Pregnancy</b><br><br>Risk Summary<br>There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses <b>1.4</b> times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses <b>34</b> times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses <b>3.4</b> times the RHOD. Maternal toxicity was observed in rats at doses <b>347</b> times the RHOD, and a maternal no observed adverse effect level (NOAEL) was |

<sup>4</sup> NDA 202872/S002 labeling approved 7/20/2018, accessed via:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/202872s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202872s002lbl.pdf)

<sup>5</sup> NDA 208219 was approved 2/22/2019. Labeling is not yet published at Drugs@FDA.

<sup>6</sup> NDA 210565 labeling approved 8/22/2018, accessed via:

[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210565s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210565s000lbl.pdf)

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>established at <b>34</b> times the RHOD. (b) (4)</p> <p>[REDACTED]</p> <p>the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|  | <p><u>Data</u></p> <p><i>Animal Data</i></p> <p>Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (<b>1.4</b> times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (<b>5.6</b> times the RHOD). At 3 mg/kg (<b>41</b> times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (<b>83</b> times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.</p> <p>Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (<b>34</b> times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (<b>347</b> times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (<b>695</b> times the RHOD). The NOAEL for developmental toxicity in rats</p> |

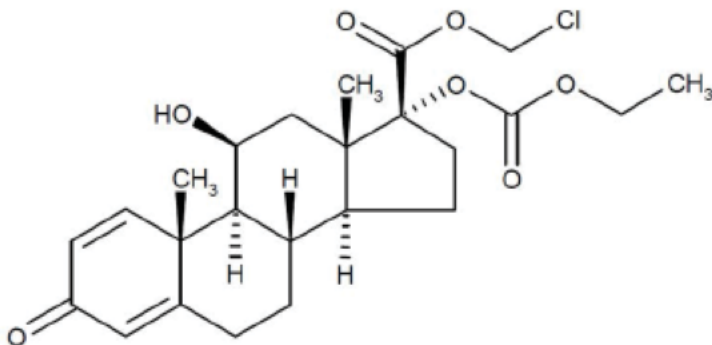


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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                               | <p>was 0.5 mg/kg (<b>3.4</b> times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.</p> <p>A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (<b>3.4</b> times the clinical dose), reduced survival was observed in live-born offspring. Doses <math>\geq</math> 5 mg/kg (<b>34</b> times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses <math>\geq</math> 50 mg/kg (<b>347</b> times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.</p> |
| <p><b>8.2 Lactation</b></p> <p>(b) (4)</p>                                                                                                                                                                                                                                                                                                                                                    | <p><b>8.2 Lactation</b></p> <p>There are no data on the presence of loteprednol etabonate in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for <b>EYSUVIS</b> and any potential adverse effects on the breastfed infant from <b>EYSUVIS</b>.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p><b>12.3 Pharmacokinetics</b></p> <p>Loteprednol etabonate is lipid soluble and can penetrate into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon in vivo and in vitro preclinical metabolism studies, loteprednol etabonate</p> | <p>[No changes; noted here for context]</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

|                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>undergoes extensive metabolism to inactive carboxylic acid metabolites, PJ-91 and PJ-90.</p> <p>Following four times a day bilateral topical ocular dosing of EYSUVIS for 14 days in healthy subjects, the plasma concentrations of loteprednol etabonate were below the limit of quantitation (1 ng/mL) at all timepoints.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>13 NONCLINICAL TOXICOLOGY</b></p> <p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p>(b) (4)</p>                                                                                                                                                                                                     | <p><b>13 NONCLINICAL TOXICOLOGY</b></p> <p><b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b></p> <p>Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic <i>in vitro</i> in the Ames test, the mouse lymphoma tk assay, or in the chromosomal aberration test in human lymphocytes, or <i>in vivo</i> in the mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).</p> |

## 2 Drug Information

### 2.1 Drug

|                       |                                                                                                                                                                                       |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CAS Registry Numbers: | <ul style="list-style-type: none"> <li>82034-46-6 (for loteprednol etabonate)</li> <li>(b) (4)</li> </ul>                                                                             |
| Generic Name          | Loteprednol etabonate                                                                                                                                                                 |
| Code Names            | <ul style="list-style-type: none"> <li>KPI-121</li> <li>KPI-121 0.25%</li> </ul>                                                                                                      |
| Chemical name         | Chloromethyl 17 $\alpha$ -[(ethoxycarbonyl)oxy]- 11 $\beta$ -hydroxy-3-oxoandrosta-1,4-diene-17 $\beta$ -carboxylate                                                                  |
| Molecular formula     | C <sub>24</sub> H <sub>31</sub> ClO <sub>7</sub>                                                                                                                                      |
| Molecular Weight      | 466.96 grams per mole                                                                                                                                                                 |
| Structure             | <p><b>Figure 1: structure of loteprednol etabonate</b></p>  <p>[From NDA module 1.14 Labeling]</p> |
| Pharmacological class | corticosteroid                                                                                                                                                                        |

### 2.2 Relevant INDs, NDAs, and DMFs

- As noted above, the Applicant referenced NDA 020-583 as the listed drug.
- The Applicant referenced their active IND 117192, under which the KPI-121 was developed.
- DMFs:
  - For this NDA 210933, Kala referenced the same seven drug master files on their FDA form 356h that they previously referenced for their NDA 210565: DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) DMF # (b) (4) DMF # (b) (4)
  - Additionally, for this NDA, Kala referenced one additional master file: DMF # (b) (4)

- For each of this DMFs, statements of right of reference were provided in NDA module 1.4 (References)
- Notably, DMF (b) (4) for manufacture of the loteprednol etabonate drug substance.
- P/T defers to the Quality review team, regarding the adequacy of the DMFs to support the NDA.

**Table 1: FDA-approved NDAs for loteprednol etabonate**

| NDA #  | Applicant     | Trade name | Dose of loteprednol etabonate | Route                        | Marketing status |
|--------|---------------|------------|-------------------------------|------------------------------|------------------|
| 20583  | Bausch & Lomb | Lotemax    | 0.5%                          | Ophthalmic suspension/drops  | Prescription     |
| 20803  | Bausch & Lomb | Alrex      | 0.2%                          | Ophthalmic suspension /drops | Prescription     |
| 20841  | Bausch & Lomb | Lotemax    | 0.5%                          | Ophthalmic suspension/drops  | Prescription     |
| 50804  | Bausch & Lomb | Zylet      | 0.5% (+ 0.3% tobramycin)      | Ophthalmic suspension/drops  | Prescription     |
| 200738 | Pharmos       | Lotemax    | 0.5%                          | Ophthalmic ointment          | Discontinued     |
| 202872 | Bausch & Lomb | Lotemax    | 0.5%                          | Ophthalmic gel               | Prescription     |
| 210565 | Kala          | Inveltys   | 1%                            | Ophthalmic suspension/drops  | Prescription     |
| 208219 | Bausch & Lomb | Lotemax SM | 0.38%                         | Ophthalmic gel               | Prescription     |

*Administrative note:* Bausch & Lomb's NDA 208219 for Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% was approved on 2/22/2019, after Kala submitted this NDA 210933 (10/15/2018).

## 2.3 Drug Formulation

- From NDA module 2.3.P (Description and Composition of the Drug Product):  
*"KPI-121 0.25% is a sterile aqueous (b) (4) suspension of loteprednol etabonate (LE) for topical ophthalmic use. Each milliliter of KPI-121 0.25% contains 2.5 mg LE as the active ingredient. Inactive ingredients are glycerin, sodium citrate dihydrate, sodium chloride, poloxamer 407, edetate disodium dihydrate, citric acid, and water for injection. Benzalkonium chloride (0.01% w/v) is added as preservative. (b) (4)"*

**Table 2: Drug product formulation**

| <b>Ingredient</b>           | <b>Quality Standard</b> | <b>Function</b> | <b>Amount (mg) in each mL of KPI-121 0.25%</b> | <b>Concentration (%w/v) in KPI-121 0.25%</b> |
|-----------------------------|-------------------------|-----------------|------------------------------------------------|----------------------------------------------|
| Loteprednol etabonate       | DMF (b) (4)             | API             | 2.5                                            | 0.25                                         |
| Glycerin                    | USP-NF                  | (b) (4)         | (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                  |                 |                                                |                                              |
| Benzalkonium chloride       | USP-NF                  | Preservative    | 0.1                                            | 0.01                                         |
| Water for injection         | USP-NF                  | (b) (4)         |                                                |                                              |

API: active pharmaceutical ingredient

(b) (4)

USP-NF: United States Pharmacopeia – National Formulary

- The drug product is supplied in two configurations: a physician sample bottle (2.4 ml) and a 10 ml capacity commercial fill bottle (8.3 ml of KPI-121 0.25%)
- The drop size is reported: “The dropper bottle tip delivers approximately (b) (4) of KPI-121 0.25% per drop.”
- Review note: (b) (4)
- Under module 3.2.S.4 Control of Drug Substance – Specification<sup>7</sup>, the Applicant provided information from “DMF (b) (4)”, describing the particle size distribution:

<sup>7</sup> Internal file location:

(b) (4)

**Table 3: Particle size distribution for the loteprednol etabonate drug substance**

| Particle size distribution (percentage of diameters at or below the specified size) | Particle size specification ( (b) (4) |
|-------------------------------------------------------------------------------------|---------------------------------------|
| (b) (4)                                                                             |                                       |

## 2.4 Comments on Novel Excipients

- As noted in the table above, the excipients used in KPI-121 1% are compendial. Each of the exposures has previously been qualified.
  - The excipients were qualified by the rabbit 28-day ocular toxicology study (report # 8286658).
  - In the approved labeling for the listed drug (NDA 20583), Lotemax's excipients are "glycerin, (b) (4) edetate disodium (b) (4)" with 0.01% benzalkonium chloride preservative.
  - Notably, Inveltys™ (NDA 210565) qualifies the exposure to Poloxamer 407 (on both a mg/eye/dose basis, and on a mg/eye/day basis).

## 2.5 Comments on Impurities/Degradants of Concern

The impurities for KPI-121 0.25% are not concerning.

- The CMC team (personal communications, Zhang/McDougal, 11/2018) asked P/T to verify that acceptance criteria for (b) (4) are adequately qualified.
- With reference to previous P/T reviews (e.g., McDougal, 7/19/2018, NDA 210565), (b) (4)
- Daily exposure to (b) (4) arising from topical ocular use of Eysuvis™ are not high enough to trigger the recommendation for SAR testing, per ICH M7(R1)<sup>8</sup>.

<sup>8</sup> ICH M7(R1). Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk Guidance for Industry Accessed via: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm347725.pdf>

## 2.6 Proposed Clinical Population and Dosing Regimen

The Applicant has proposed:

- Indication: “for the temporary relief of the signs and symptoms of dry eye disease”
- Dosage and administration: Instill one to two drops into each eye four times a day for two weeks.

## 2.7 Regulatory Background

Kala developed KPI-121 (loteprednol etabonate ophthalmic suspension) under IND 117192. Arising from this IND, Invelyts™ (the 1% formulation) was approved under NDA 210565. Arising from the same IND, this NDA 210993 is for Eysuvis™ (the 0.25% formulation).

- A pre-IND meeting was held April 4, 2013. The original IND 117192 was submitted December 23, 2013.
- NDA 210565 was submitted April 24, 2017 and approved August 22, 2018.
- This NDA 210933 was submitted October 15, 2018.

## 3 Studies Submitted

### 3.1 Study Reviewed

| Laboratory Report # | Study Title                                                                                                       | Kala summary report # |
|---------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------|
| 2012-177            | Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with Three Formulations | KPI-121-T059          |

### 3.2 Studies Not Reviewed

The following studies were previously submitted by the Applicant to their NDA 210565, and have already been reviewed by P/T (McDougal, 7/19/2018, NDA 210565):

**Table 4: List of previously submitted nonclinical studies, resubmitted to NDA 210933**

| Laboratory Report # | Study Title                                                                                           | <sup>a</sup> Kala summary report # |
|---------------------|-------------------------------------------------------------------------------------------------------|------------------------------------|
| 8286656             | Validation of a Method for the Determination of KPI-121 in Rabbit Plasma by HPLC with MS/MS Detection | [none]                             |



|          |                                                                                                                                       |              |
|----------|---------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 2012-206 | Pharmacokinetics of Loteprednol Etabonate (LE) in Aqueous Humor Following Topical Dosing with Formulations of Various Concentrations  | KPI-121-T001 |
| 2013-030 | Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with Either One of Two LE Test Formulations | KPI-121-T003 |
| 2013-150 | Pharmacokinetics of Loteprednol (1%) of Various Particle Size Administered Topically in a MPP Formulation                             | KPI-121-T022 |
| 8286658  | 28-Day Ocular Instillation Toxicity and Toxicokinetic Study with KPI-121 in Rabbits                                                   | KPI-121-T005 |

<sup>a</sup> Aside from the analytical validation report (# 8286656), Kala provided a short summary report separate from each laboratory report. These summaries were fully reviewed, toward understanding the Applicant's interpretation of the study results. For the IND, Kala's reports were included in the same pdf file as the laboratory report. For the NDA, Kala provided their summary reports in separate pdf files from the laboratory report.

*Administrative note:* Kala submitted a nonclinical study (report # 2013-068) to NDA 210565 and the referenced parent IND 117192, but not to this NDA 210933. This reviewer concurs that the formulations tested are not relevant to this NDA, and notes for the record that the results raised no new safety concerns (either for Inveltys or Eysuvis).

### 3.3 Previous Reviews Referenced

- For IND 117192: the minutes of the pre-IND meeting (Puglisi, 4/26/2013) and the P/T reviews (McDougal; 1/23/2014, 7/28/2017, 8/30/2017) are referenced.
- For NDA 210565, two P/T reviews are referenced (McDougal; 7/19/2018, 8/01/2018)
- This NDA lists NDA 020583 (Lotemax). NDA 20583 was originally submitted by Pharmos; the current Applicant is Bausch and Lomb. For completeness-of-record, the public availability of a redacted version of the P/T review for the original NDA 20583 submission is noted<sup>9</sup>. The NDA 20583 PT review was not necessary to support the safety of KPI-121.
- The P/T review conducted to support PLLR labeling for loteprednol etabonate (NDA 202872/S02) is referenced.

<sup>9</sup> NDA 20583. P/T review by Dr. David A. Shriver, available as two parts via: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/98/20583\\_LOTEMAX\\_pharmr\\_P1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20583_LOTEMAX_pharmr_P1.pdf) and [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/98/20583\\_LOTEMAX\\_pharmr\\_P2.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20583_LOTEMAX_pharmr_P2.pdf)



## 4 Pharmacology

- The Applicant did not submit nonclinical primary pharmacology, secondary pharmacology, or safety pharmacology studies with KPI-121.
- P/T defers to the review team regarding the adequacy of the clinical trials to demonstrate pharmacological activity for KPI-121 0.25%.
- The NDA is relying on the Agency's finding of safety and effectiveness for Lotemax® (NDA 20583), as described in published labeling.

## 5 Pharmacokinetics/ADME/Toxicokinetics

- The Applicant's proposed labeling, Section 12.3 Pharmacokinetics, proposes *"Following four times a day bilateral topical ocular dosing of EYSUVIS for 14 days in healthy subjects, the plasma concentrations of loteprednol etabonate were below the limit of quantitation (1 ng/mL) at all timepoints."*
- The rabbit general toxicology study (report # 8286658) tested the clinical drug product, and provided toxicokinetic (TK) results. None of the pharmacokinetic (PK) rabbit studies report testing the clinical formulation of the Eysuvis™ drug product.
  - For some test articles, the formulation was not reported.
  - For other test articles, the reports note that different excipients, strengths of loteprednol etabonate, and particle sizes of loteprednol etabonate than the clinical formulation.
- Following single topical ocular doses, loteprednol etabonate was detected in the rabbit eye structures (including aqueous humor and retina).

### 5.1 Review notes regarding the previously reviewed PK results

- Under IND 117192, Kala conducted multiple rabbit TK studies to investigate different formulations of loteprednol etabonate. Their goal was to use mucous penetrating particle (MPP) technology to manufacture mucus penetrating particles (MPP) of the drug substance. The nonclinical studies did not test the clinical formulation of Eysuvis™.
- The PK study studies previously reviewed for NDA 210565 (McDougal, 7/19/2018, NDA 210565) were not re-reviewed. Briefly:
  - The analytical method study (report # 8286656) validated a detection range of 0.100 to 200 ng/ml for loteprednol etabonate in rabbit plasma.
  - A rabbit ocular distribution study (report # 2013-030) compared two formulations, one of which had the same strength (0.25%) of loteprednol etabonate as the Eysuvis™ clinical drug product.
    - Following a single topical ocular dose (50 µl/eye) administered to both eyes (OU), distribution was cornea > aqueous humor > retina > plasma
    - Loteprednol etabonate was detected immediately (at the 5-minute time point) in all tissues (including retina and plasma) after a single topical ocular dose, but cleared rapidly.

- For the 0.25% formulation, loteprednol was detected in 5/6 retinas at 5 minutes, and in most retinas from 15 minutes to 1 hour. It was not detected in any retinas at 3 or 6 hours.
- No ocular irritation was observed.
- o Another rabbit ocular distribution study (report # 2013-068) tested three different formulations of loteprednol etabonate 0.1% against Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%.
- o A third rabbit ocular distribution study (report # 2012-206) tested four different strengths (0.4 to 1.0%) of loteprednol etabonate ophthalmic suspension.
- o A fourth rabbit ocular distribution study (report # 2013-150) tested 5 different formulations of loteprednol etabonate ophthalmic suspension 1%. Each had a different range of particle sizes.
  - Distribution was cornea > palpebral conjunctiva > aqueous humor > retina > plasma.
  - Smaller particle size correlated with higher C<sub>max</sub> values for the cornea, aqueous humor, conjunctiva, and retina.
  - No treatment-related ocular irritation was detected.

## 5.2 Review of report # 2012-177

- For NDA 210933, Kala submitted one additional nonclinical study (not previously submitted to NDA 210565). P/T has fully reviewed this study:

|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                           |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Study title    | <b>Pharmacokinetics of Loteprednol Etabonate (LE) in Ocular Tissues Following Topical Dosing with Three Formulations</b>                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                           |
| Report #s      | <ul style="list-style-type: none"> <li>• 2012-177 (laboratory study #)</li> <li>• (b) (4) (Sponsor study #)</li> <li>• KPI-121-T059 (Kala's summary)</li> </ul>                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                           |
| Key findings   | <ul style="list-style-type: none"> <li>• Three formulations of loteprednol etabonate were compared against Lotemax® 0.5%. Excipients were not reported, limiting the value of this study.</li> <li>• Following a bilateral dosing with single topical ocular drop, none of the test articles caused ocular irritation.</li> <li>• The three formulations resulted in slightly higher exposure (by C<sub>max</sub> and AUC) in the aqueous humor and retina, compared to Lotemax® 0.5%</li> </ul> |                                                                                                                                           |
| Report details | Study laboratory                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | (b) (4)                                                                                                                                   |
|                | Report date                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | August 5, 2013                                                                                                                            |
|                | Report status                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Signed; not GLP                                                                                                                           |
|                | NDA location                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Module 4.2.2.2 (Nonclinical study reports: Pharmacokinetics: Absorption)<br><a href="#">\\cdsesub1\evsprod\nda210933\0001\m4\42-stud-</a> |

|               |                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               |                                    | <a href="#">rep\422-pk\4222-absorp\2012-177\2012-177.pdf</a> and <a href="#">\cdsesub1\evsprod\nda210933\0001\m4\42-stud-rep\422-pk\4222-absorp\2012-177\kpi-121-t-059.pdf</a>                                                                                                                                                                                                                                                                                                                     |
| Methods notes | Species and group size             | 15 male New Zealand White (NZW) rabbits/formulation                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|               | Four different formulations:       | <ul style="list-style-type: none"> <li>• KPI-121 0.5% (b) (4)</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• [REDACTED] <ul style="list-style-type: none"> <li>○ <i>Review note:</i> the documents submitted to the NDA do not explicitly state that the concentration of loteprednol etabonate was 0.5% for this formulation. Based on the PK results, this reviewer infers that this formulation was also 0.5%.</li> </ul> </li> <li>• Lotemax® 0.5% (commercial formulation)</li> </ul> |
|               | KPI-121 particle size distribution | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|               | Dosing                             | <ul style="list-style-type: none"> <li>• For each rabbit, both eyes were dosed once by topical ocular administration of 50 µl using a calibrated pipette.</li> <li>• Animals were restrained for 2 minutes post-dose to prevent head shaking or pawing at the eyes.</li> <li>• Ocular irritation was evaluated and scored (using the Draize Eye Irritation Scoring Scale)</li> </ul>                                                                                                               |
|               | Tissue harvest                     | <ul style="list-style-type: none"> <li>• At five time points (0.5, 1, 2, 4, and 8 hours), 3 rabbits/test article were sacrificed. Aqueous</li> </ul>                                                                                                                                                                                                                                                                                                                                               |

|                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | humor, cornea, palpebral conjunctiva, and retina samples were collected. <ul style="list-style-type: none"><li>Retina samples were collected via center punch biopsy.</li><li>Tissues were frozen until analysis (LC/MS/MS)</li></ul> |               |                              |                       |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------------------------------|-----------------------|---------------|------------------------------|---------------|---------------|-----|------|-----|-----|------|---|------|-----|------|------|---|------|------|-----|------|---|-------|------|-----|------|---|--------|------|------|-------|---------|-----|------|-----|-----|------|---|------|-----|------|------|---|------|------|-----|------|---|-------|------|------|-------|---|--------|------|------|-------|-----|------|------|-----|------|---|------|-----|-----|------|---|------|-----|-----|------|---|-------|-----|-----|------|---|-------|-----|-----|-------|-----|------|-----|-----|------|---|------|-----|-----|------|---|------|------|-----|------|---|-------|------|------|------|---|-------|------|-----|-------|
| Safety results | <ul style="list-style-type: none"><li>No ocular irritation was noted for any rabbit.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                       |               |                              |                       |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
| Results        | <ul style="list-style-type: none"><li>A single dose of each formulation resulted in detectable exposure to the retina, out to the last time point measured (8 hours post-dose).</li><li>Across the formulations, exposure was conjunctiva &gt; cornea &gt; aqueous humor &gt; retina (as expected for a topical ocular drop)</li></ul> <p><b>Table 5: Rabbit tissue concentration data (report # 2012-177)</b></p> <table><tr><th>Formulation</th><th>Time point (hr)</th><th>Aqueous humor (ng/ml)</th><th>Cornea (ng/g)</th><th>Palpebral conjunctiva (ng/g)</th><th>Retina (ng/g)</th></tr><tr><td rowspan="5">Lotemax® 0.5%</td><td>0.5</td><td>6.49</td><td>296</td><td>296</td><td>3.21</td></tr><tr><td>1</td><td>4.07</td><td>110</td><td>81.1</td><td>1.54</td></tr><tr><td>2</td><td>1.32</td><td>85.1</td><td>139</td><td>1.40</td></tr><tr><td>4</td><td>0.374</td><td>77.1</td><td>270</td><td>1.19</td></tr><tr><td>8</td><td>0.0496</td><td>14.0</td><td>23.9</td><td>0.421</td></tr><tr><td rowspan="15">(b) (4)</td><td>0.5</td><td>11.4</td><td>503</td><td>206</td><td>4.56</td></tr><tr><td>1</td><td>7.68</td><td>214</td><td>86.9</td><td>3.80</td></tr><tr><td>2</td><td>2.66</td><td>97.7</td><td>294</td><td>2.04</td></tr><tr><td>4</td><td>0.306</td><td>42.0</td><td>64.6</td><td>0.943</td></tr><tr><td>8</td><td>0.0485</td><td>16.8</td><td>20.3</td><td>0.270</td></tr><tr><td>0.5</td><td>23.4</td><td>1070</td><td>989</td><td>7.95</td></tr><tr><td>1</td><td>15.6</td><td>423</td><td>494</td><td>9.07</td></tr><tr><td>2</td><td>4.66</td><td>312</td><td>661</td><td>2.83</td></tr><tr><td>4</td><td>0.586</td><td>232</td><td>185</td><td>2.18</td></tr><tr><td>8</td><td>0.113</td><td>174</td><td>143</td><td>0.565</td></tr><tr><td>0.5</td><td>11.7</td><td>416</td><td>440</td><td>3.73</td></tr><tr><td>1</td><td>9.15</td><td>396</td><td>400</td><td>3.96</td></tr><tr><td>2</td><td>2.47</td><td>69.5</td><td>116</td><td>2.31</td></tr><tr><td>4</td><td>0.305</td><td>44.4</td><td>82.3</td><td>1.07</td></tr><tr><td>8</td><td>0.112</td><td>61.4</td><td>313</td><td>0.472</td></tr></table> |                                                                                                                                                                                                                                       | Formulation   | Time point (hr)              | Aqueous humor (ng/ml) | Cornea (ng/g) | Palpebral conjunctiva (ng/g) | Retina (ng/g) | Lotemax® 0.5% | 0.5 | 6.49 | 296 | 296 | 3.21 | 1 | 4.07 | 110 | 81.1 | 1.54 | 2 | 1.32 | 85.1 | 139 | 1.40 | 4 | 0.374 | 77.1 | 270 | 1.19 | 8 | 0.0496 | 14.0 | 23.9 | 0.421 | (b) (4) | 0.5 | 11.4 | 503 | 206 | 4.56 | 1 | 7.68 | 214 | 86.9 | 3.80 | 2 | 2.66 | 97.7 | 294 | 2.04 | 4 | 0.306 | 42.0 | 64.6 | 0.943 | 8 | 0.0485 | 16.8 | 20.3 | 0.270 | 0.5 | 23.4 | 1070 | 989 | 7.95 | 1 | 15.6 | 423 | 494 | 9.07 | 2 | 4.66 | 312 | 661 | 2.83 | 4 | 0.586 | 232 | 185 | 2.18 | 8 | 0.113 | 174 | 143 | 0.565 | 0.5 | 11.7 | 416 | 440 | 3.73 | 1 | 9.15 | 396 | 400 | 3.96 | 2 | 2.47 | 69.5 | 116 | 2.31 | 4 | 0.305 | 44.4 | 82.3 | 1.07 | 8 | 0.112 | 61.4 | 313 | 0.472 |
| Formulation    | Time point (hr)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Aqueous humor (ng/ml)                                                                                                                                                                                                                 | Cornea (ng/g) | Palpebral conjunctiva (ng/g) | Retina (ng/g)         |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
| Lotemax® 0.5%  | 0.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 6.49                                                                                                                                                                                                                                  | 296           | 296                          | 3.21                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4.07                                                                                                                                                                                                                                  | 110           | 81.1                         | 1.54                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1.32                                                                                                                                                                                                                                  | 85.1          | 139                          | 1.40                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.374                                                                                                                                                                                                                                 | 77.1          | 270                          | 1.19                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.0496                                                                                                                                                                                                                                | 14.0          | 23.9                         | 0.421                 |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
| (b) (4)        | 0.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 11.4                                                                                                                                                                                                                                  | 503           | 206                          | 4.56                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 7.68                                                                                                                                                                                                                                  | 214           | 86.9                         | 3.80                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 2.66                                                                                                                                                                                                                                  | 97.7          | 294                          | 2.04                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.306                                                                                                                                                                                                                                 | 42.0          | 64.6                         | 0.943                 |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.0485                                                                                                                                                                                                                                | 16.8          | 20.3                         | 0.270                 |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 0.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 23.4                                                                                                                                                                                                                                  | 1070          | 989                          | 7.95                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 15.6                                                                                                                                                                                                                                  | 423           | 494                          | 9.07                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 4.66                                                                                                                                                                                                                                  | 312           | 661                          | 2.83                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.586                                                                                                                                                                                                                                 | 232           | 185                          | 2.18                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.113                                                                                                                                                                                                                                 | 174           | 143                          | 0.565                 |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 0.5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 11.7                                                                                                                                                                                                                                  | 416           | 440                          | 3.73                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 9.15                                                                                                                                                                                                                                  | 396           | 400                          | 3.96                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 2.47                                                                                                                                                                                                                                  | 69.5          | 116                          | 2.31                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.305                                                                                                                                                                                                                                 | 44.4          | 82.3                         | 1.07                  |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |
|                | 8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.112                                                                                                                                                                                                                                 | 61.4          | 313                          | 0.472                 |               |                              |               |               |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |     |      |   |        |      |      |       |         |     |      |     |     |      |   |      |     |      |      |   |      |      |     |      |   |       |      |      |       |   |        |      |      |       |     |      |      |     |      |   |      |     |     |      |   |      |     |     |      |   |       |     |     |      |   |       |     |     |       |     |      |     |     |      |   |      |     |     |      |   |      |      |     |      |   |       |      |      |      |   |       |      |     |       |

|                                                    |                                                                 |                          |                  |        |                              |
|----------------------------------------------------|-----------------------------------------------------------------|--------------------------|------------------|--------|------------------------------|
| Lotemax®<br>0.5% ocular<br>distribution<br>results | <b>Table 6: Lotemax® 0.5% ocular distribution PK parameters</b> |                          |                  |        |                              |
|                                                    | Lotemax®<br>0.5% PK<br>parameters                               | Palpebral<br>Conjunctiva | Aqueous<br>Humor | Cornea | Retina<br>(center-<br>punch) |
|                                                    | T <sub>max</sub><br>(hours)                                     | 0.5                      | 0.5              | 0.5    | 0.5                          |
|                                                    | C <sub>max</sub> (ng/g<br>or ng/mL)                             | 296                      | 6.49             | 296    | 3.21                         |
|                                                    | t <sub>1/2</sub><br>elimination<br>(hours)                      | 2.05                     | 1.28             | 2.37   | 3.69                         |
|                                                    | AUC <sub>0-last</sub><br>(ng*h/g or<br>ng*h/mL)                 | 1270                     | 9.50             | 617    | 9.26                         |
|                                                    | AUC <sub>0-inf</sub><br>(ng*h/g or<br>ng*h/mL)                  | 1340                     | 9.59             | 665    | 11.5                         |
| KPI-121<br>0.5% ocular<br>distribution<br>results  | <b>Table 7: KPI-121 0.5% ocular distribution PK parameters</b>  |                          |                  |        |                              |
|                                                    | KPI-121<br>0.5% PK<br>parameters                                | Palpebral<br>Conjunctiva | Aqueous<br>Humor | Cornea | Retina<br>(center-<br>punch) |
|                                                    | T <sub>max</sub><br>(hours)                                     | 0.5                      | 0.5              | 0.5    | 1.0                          |
|                                                    | C <sub>max</sub> (ng/g<br>or ng/mL)                             | 989                      | 23.4             | 1070   | 9.07                         |
|                                                    | t <sub>1/2</sub><br>elimination<br>(hours)                      | 3.31                     | 1.01             | 7.40   | 2.49                         |
|                                                    | AUC <sub>0-last</sub><br>(ng*h/g or<br>ng*h/mL)                 | 2700                     | 32.4             | 2360   | 22.7                         |
|                                                    | AUC <sub>0-inf</sub><br>(ng*h/g or<br>ng*h/mL)                  | 3380                     | 32.6             | 4220   | 24.7                         |

(b) (4)

**Table 8: (b) (4) LE-MPP 0.5% ocular distribution PK parameters**

| (b) (4)<br>LE-MPP 0.5%<br>PK<br>parameters      | Palpebral<br>Conjunctiva | Aqueous<br>Humor | Cornea | Retina<br>(center-<br>punch) |
|-------------------------------------------------|--------------------------|------------------|--------|------------------------------|
| T <sub>max</sub><br>(hours)                     | 2.0                      | 0.5              | 0.5    | 0.5                          |
| C <sub>max</sub> (ng/g<br>or ng/mL)             | 294                      | 11.4             | 503    | 4.56                         |
| t <sub>1/2</sub><br>elimination<br>(hours)      | 1.64                     | 0.974            | 2.44   | 2.08                         |
| AUC <sub>0-last</sub><br>(ng*h/g or<br>ng*h/mL) | 843                      | 16.4             | 718    | 11.6                         |
| AUC <sub>0-inf</sub><br>(ng*h/g or<br>ng*h/mL)  | 891                      | 16.5             | 777    | 12.4                         |

(b) (4)

**Table 9: (b) (4) LE-MPP (concentration not reported) ocular distribution PK parameters**

| (b) (4)<br>LE-MPP PK<br>parameters              | Palpebral<br>Conjunctiva | Aqueous<br>Humor | Cornea | Retina<br>(center-<br>punch) |
|-------------------------------------------------|--------------------------|------------------|--------|------------------------------|
| T <sub>max</sub><br>(hours)                     | 0.5                      | 0.5              | 0.5    | 1.0                          |
| C <sub>max</sub> (ng/g<br>or ng/mL)             | 440                      | 11.7             | 416    | 3.96                         |
| t <sub>1/2</sub><br>elimination<br>(hours)      | NC                       | 1.15             | 3.68   | 2.70                         |
| AUC <sub>0-last</sub><br>(ng*h/g or<br>ng*h/mL) | 1570                     | 17.6             | 865    | 12.5                         |
| AUC <sub>0-inf</sub><br>(ng*h/g or<br>ng*h/mL)  | NC                       | 17.7             | 1190   | 14.3                         |

## 6 General Toxicology

The Applicant submitted one toxicology study for KPI-121: report # 8286658. The Applicant also provided a separate report (report # KPI-121-T-005 Technical Report) describing the test article characterization. This study was reviewed previously (McDougal, 7/19/2018, NDA 210565), and was not re-reviewed. Briefly:

- Groups of 3/sex New Zealand White (NZW) rabbits were dosed with 0 or 1% KPI-121 four times daily (QID) in both eyes for 28 days. The test article was well-tolerated, and no dose-limiting toxicities were observed.
- The clinical formulation was tested, differing only in the amounts of loteprednol etabonate (1%, 10 mg/ml) and Poloxamer 407 (b) (4) [Review note: Poloxamer 407 (b) (4) This is acceptable from a nonclinical perspective, and is not expected to affect the results or study interpretation.]
- Treatment-related pharmacological activity was observed at the single test dose:
  - decreased body weight (-7% by D29) for males and females
  - Higher mean corpuscular volume and mean corpuscular hemoglobin (males)
  - Decreased absolute lymphocyte counts (both sexes)
  - Higher glucose (males)
  - Higher triglycerides (both sexes)
  - Higher aspartate aminotransferase and alanine aminotransferase (females)
  - Organ weight changes: adrenal, spleen, and thymus (both sexes); prostate/seminal vesicle gland
  - Histopathology (both sexes): adrenal cortex atrophy; eyelid decreased anagen hair follicles
- The authors considered the effects on spleen and thymus correlated with decreased lymphocyte counts, and to be potentially adverse. The authors also considered the adrenal cortical atrophy to be potentially adverse. This reviewer concurs; therefore, a no observed adverse effect level (NOAEL) was not identified.
- Loteprednol etabonate was detected in plasma (b) (4) Plasma TK parameters were calculated.

## 7 Genetic Toxicology

The Applicant did not conduct genetic toxicology studies. The NDA is relying on the Agency's finding of safety and effectiveness for Lotemax® (NDA 20583), as described in published labeling. The labeling for Lotemax® (NDA 20583) reports that loteprednol etabonate was not genotoxic in the Ames assay, the mouse lymphoma tk assay, a chromosomal aberration assay in human lymphocytes, or in the *in vivo* mouse micronucleus assay.



## 8 Carcinogenicity

The Applicant did not conduct carcinogenicity studies for KPI-121. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. P/T concurs that carcinogenicity studies are not warranted to support the indicated duration of use for this NDA (i.e. 2 weeks).

## 9 Reproductive and Developmental Toxicology

The Applicant did not conduct reproductive toxicology, developmental toxicology, or fertility studies. The NDA is relying on the Agency's finding of safety and effectiveness for Lotemax® (NDA 20583), as described in published labeling.

DTOP approved detailed PLLR-complaint labeling for Lotemax® under NDA 202872 on 7/20/2018. Notably, this version of the PLLR-language for loteprednol etabonate was not incorporated into the labeling for Kala's NDA 210565 (which was submitted 10/24/2017).

## 11 Integrated Summary and Safety Evaluation

- The NDA for Eysuvis™ is submitted under the 505(b)(2) pathway, listing NDA 20583 for Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5%.
- PLLR review of the nonclinical studies supporting labeling was recently conducted, under NDA 202872 for Lotemax® (loteprednol etabonate ophthalmic gel) 0.5%.
- For labeling, adjustment is warranted based on dosage, administration, and drop volume of the commercial drug product.
- For Eysuvis™, the strength is 0.25% (2.5 mg/ml). the Applicant proposed a dosage and administration of one to two drops in each eye, four times a day (QID) for two weeks.

### 11.1 Supporting bridge for the 505(b)(2) approach

- Kala used the same bridging approach for both NDAs (NDA 210565 for Inveltys™ and NDA 210933 for Eysuvis™). From a nonclinical perspective, both rely on the listed NDA 20583 for the same P/T information for the **loteprednol etabonate drug substance**: mechanism of action, metabolism, genotoxicity, developmental and reproductive toxicity, fertility, and decisions that particular nonclinical studies (lactation, carcinogenicity) are not warranted to support safety.
- The route of administration is the same for both (topical ocular). (b) (4)  

- Nonclinical safety support for both NDAs was conducted under the same IND. The same pivotal toxicology study report and important PK study reports were submitted to both NDAs.

- From a nonclinical perspective, the nonclinical bridge to NDA 20583 (Lotemax®) is based on:
  - The drug substance identity and route of exposure being identical
  - Kala's drug substance's doses being covered by the study doses described in labeling for the listed drug (under sections 8 and 13).
- To support the safety of the loteprednol etabonate drug product, Kala conducted their own rabbit pharmacokinetic studies (which included ocular distribution), a rabbit ocular toxicology study, and clinical trials.

## 11.2 Dose margin calculations

To the extent feasible, nonclinical clinical labeling for the same drug substance should be consistent, to help readers understand and compare labeling.

**Table 10: Daily dose of loteprednol etabonate for Eysuvis™ compared to other recent loteprednol etabonate labeling**

| Trade name                                       | Lotemax                                                           | Lotemax SM                                                 | Inveltys™                                                    | Eysuvis™                                                           |
|--------------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------|
| NDA #                                            | 202872                                                            | 208219                                                     | 210565                                                       | 210933                                                             |
| Strength of loteprednol etabonate (%)            | 0.5%                                                              | 0.38%                                                      | 1%                                                           | 0.25%                                                              |
| Strength (µg/µl)                                 | 5                                                                 | 3.8                                                        | 10                                                           | 2.5                                                                |
| Dosage and administration                        | One or two drops in one eye, four times a day (QID) for two weeks | One drop in one eye, three times daily (TID) for two weeks | One or two drops in one eye, twice daily (BID) for two weeks | One to two drops in each eye, four times a day (QID) for two weeks |
| # of drops/eye/day <sup>A</sup>                  | 8                                                                 | 3                                                          | 4                                                            | 8                                                                  |
| # of drops/person/day                            | 16                                                                | 3                                                          | 4                                                            | 16                                                                 |
| Drop size (µl)                                   | (b) (4)                                                           |                                                            |                                                              |                                                                    |
| Dose (µg) /person/day                            | (b) (4)                                                           |                                                            |                                                              |                                                                    |
| Dose (mg) /person/day                            |                                                                   |                                                            |                                                              |                                                                    |
| Daily dose (mg/m <sup>2</sup> /day) <sup>B</sup> |                                                                   |                                                            |                                                              |                                                                    |

<sup>A</sup> Assuming two drops/dose are given when labeling specifies one or two drops per dose.

<sup>B</sup> Assuming a reference adult human body weight of 60 kg, and using a body surface area correction factor (CF) of 37 to convert from mg/kg to mg/m<sup>2</sup> for patients.

- P/T proposes to align the nonclinical sections of labeling for Inveltys™ and Eysuvis™.
  - The current labeling for Inveltys does not report nonclinical dose margins. However, P/T expects to update its labeling, for consistency with Eysuvis™ (as well as Lotemax, and Lotemax SM)
  - From a nonclinical perspective, the (b) (4) % difference in drop sizes between Inveltys (b) (4) and Eysuvis™ (b) (4) is comparable, in the context of the labeled dosage and administration. Administering two drops per dose results in a volume larger than can be accommodated by the eye, and some spillage is expected.
  - P/T's approach is to round the drop volume for Eysuvis™ from (b) (4) to (b) (4). This rounding approach avoids presenting slightly different numbers across labels.
  - Therefore, the daily dose of (b) (4) mg/m<sup>2</sup>/day is used to calculate dose margins for Eysuvis™.

**Table 11: Dose margins for labeling**

| Species | Oral daily dose (mg/kg) | Oral daily dose (mg/m <sup>2</sup> ) <sup>A</sup> |                                                                                 |                                                                                 | P/T dose margin for                                                         |                                                                               |
|---------|-------------------------|---------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|
|         |                         |                                                   | Lotemax Gel (0.5%; NDA 202872): clinical dose of (b) (4) mg/m <sup>2</sup> /day | Lotemax SM (0.38%, NDA 208219): clinical dose of (b) (4) mg/m <sup>2</sup> /day | Inveltys™ (1%; NDA 210565): clinical dose of (b) (4) mg/m <sup>2</sup> /day | Eysuvis™ (0.25%, NDA 210933): clinical dose of (b) (4) mg/m <sup>2</sup> /day |
| Rabbit  | 0.1                     | 1.2                                               | 1.2                                                                             | 4.26x                                                                           | 1.4 x                                                                       | 1.4 x                                                                         |
|         | 0.4                     | 4.8                                               | 4.8                                                                             | 17.0x                                                                           | 5.6 x                                                                       | 5.6 x                                                                         |
|         | 0.5                     | 6                                                 | 6                                                                               | 21.3x                                                                           | 7.0 x                                                                       | 7.0 x                                                                         |
|         | 3.0                     | 36                                                | 36                                                                              | 128.0x                                                                          | 41 x                                                                        | 41 x                                                                          |
|         | 6                       | 72                                                | 72                                                                              | 256.0x                                                                          | 83 x                                                                        | 83 x                                                                          |
|         | 12.5                    | 150                                               | 150                                                                             | 533.4x                                                                          | 174 x                                                                       | 174 x                                                                         |
|         | 25                      | 300                                               | 300                                                                             | 1066.8x                                                                         | 347 x                                                                       | 347 x                                                                         |
|         | 50                      | 600                                               | 600                                                                             | 2133.7 x                                                                        | 695 x                                                                       | 695 x                                                                         |
|         | 100                     | 1200                                              | 1200                                                                            | 4267.4 x                                                                        | 1390 x                                                                      | 1390 x                                                                        |
| Rat     | 0.5                     | 3                                                 | 3                                                                               | 10.6 x                                                                          | 3.4 x                                                                       | 3.4 x                                                                         |
|         | 5.0                     | 30                                                | 30                                                                              | 106.6 x                                                                         | 34 x                                                                        | 34 x                                                                          |

|  |     |     |     |          |       |       |
|--|-----|-----|-----|----------|-------|-------|
|  | 25  | 150 | 150 | 533.4 x  | 174 x | 174 x |
|  | 50  | 300 | 300 | 1066.8 x | 347 x | 347 x |
|  | 100 | 600 | 600 | 2133.7 x | 695 x | 695 x |

<sup>A</sup> Based on correction factors of 6 for the rat, and 12 for the rabbit, to convert the dose from mg/kg to mg/m<sup>2</sup>.

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/s/  
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