CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210565Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210565
Priority or Standard	Standard
Submit Date(s)	October 24, 2017
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Division / Office	DTOP/OAP
Reviewer Name(s)	Martin P Nevitt, M.D., M.P.H.
Review Completion Date	August 1, 2018
Established Name	Loteprednol etabonate ophthalmic suspension, 1%
(Proposed) Trade Name	INVELTYS
Therapeutic Class	Corticosteroid
Applicant	Kala Pharmaceuticals, Inc.
Formulation(s)	Topical sterile suspension
Dosing Regimen	One to two drops into the affected eye twice daily beginning the day after surgery and through two weeks after surgery
Indication(s)	Treatment of post-operative pain and inflammation following ocular surgery
Intended Population(s)	Treatment of post-operative pain and inflammation following ocular surgery

Template Version: March 6, 2009

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

1.1 Recommendation on Regulatory Action

INVELTYS, also referred to as KPI-121 within this review, is recommended for approval for the treatment of post-operative pain and inflammation following ocular surgery with the edits to the labeling attached at the end of this review.

1.2 Risk Benefit Assessment

INVELTYS has been shown to be effective for the treatment of post-operative pain and inflammation following ocular surgery based on two adequate and well controlled clinical trials.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The results from the clinical development program for KPI-121 ophthalmic suspension 1%, administered as 1 to 2 drops to the affected eye twice daily for 2 weeks following surgery, is safe and effective for the treatment of post-operative inflammation and pain following ocular surgery.

A risk management plan is not necessary given the known risks of this class of products (such as cataract formation and the increase in Intraocular Pressure (IOP)).

1.4 Recommendations for Postmarket Requirements and Commitments

There are no Post-Marketing Requirements or Commitments recommended.

2 INTRODUCTION AND REGULATORY BACKGROUND

Kala Pharmaceuticals is relying on the FDA's findings of safety and effectiveness for the approved listed drug NDA 20-583 Lotemax® (loteprednol etabonate ophthalmic suspension) 0.5% to support the approved labeling as well as nonclinical literature to support nonclinical data in this 505(b)(2) submission.

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

2.1 Product Information

2.2 Tables of Currently Available Treatments for Proposed Indications

Loteprednol etabonate approved products

NDA	Drug Tradename	Formulation	Indication
20503	Loteprednol etabonate ophthalmic suspension, 0.5%	suspension	Post-operative inflammation following (b) (4)

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

2.3 Availability of Proposed Active Ingredient in the United States

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

2.4 Important Safety Issues With Consideration to Related Drugs

INVELTYS[T] as with other ophthalmic corticosteroids, is contradicted in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in myocbacteria infection of the eye and fungal diseases of ocular structures.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

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

April 4, 2013 – Type B PIND (Pre-IND) meeting was held to discuss CMC, nonclinical and clinical questions.

June 15, 2015 – Type C meeting was held to discuss product manufacturing, clinical development plans and given the known history of ophthalmic use of loteprednol it was agreed the measurement of endothelial cell counts would be not required.

May 5, 2017 – Type B meeting was held to agree upon the clinical and non-clinical components of the planned NDA submission.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

This submission was of sufficient quality to allow for a substantive review without requiring additional clinical information from the sponsor.

3.2 Compliance with Good Clinical Practices

The clinical studies contained in this application were conducted in accordance with International Conference on Harmonization (ICH) guidelines and Good Clinical Practice (GCP).

3.3 Financial Disclosures

Sub-Investigator	Site	Eye Enrolled in Study (b) (6)	Eye Enrolled in Study (b) (6)
(b) (6	(b) (6)		

(b) (6) was a sub-investigator at the (b) (6) was the principal investigator. was awarded stock options based on his scientific consulting activities in support of the sponsor's dry eye program. Only (b) (6) was enrolled in the studies which would not have had any influence on the data set where a total of 520 subjects were randomized at all sites.

See Section 9.4 of this review.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

INVELTYS contains 10 mg/ml of loteprednol etabonate, as a sterile preserved ophthalmic suspension.

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left com mon carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed- effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at 2:5 mg/kg/day doses, and cleft palate and umbilical hernia at50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with 2:50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of 5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and may delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with intlan1mation. There is no generally accepted explanation for phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Loteprednol etabonate is an ester corticosteroid and structurally different than other ocular corticosteroids, having a l 7a-chloromethyl ester, in lieu of a ketone group present in other ocular corticosteroids, as well as a 17 fi-etabonate group. Loteprednol etabonate binds with high affinity to the glucocorticoid receptor; any unbound loteprednol etabonate is metabolized to inactive metabolites.

4.4.2 Pharmacodynamics

Pain and inflammation after cataract surgery are associated with an immune activity in the eye. Given its anti-inflammatory properties, loteprednol etabonate is appropriate for treatment pain and inflammation after cataract surgery.

4.4.3 Pharmacokinetics

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 undergoes extensive metabolism to inactive carboxylic acid metabolites, PJ-91 and PJ-90.

Following twice-daily unilateral topical ocular dosing of INVELTYS for 14 days in humans, the plasma concentrations of loteprednol etabonate and its metabolites (PJ-91 and PJ-90) were below the limit of quantitation (1 ng/mL, 1 ng/mL, and 5 ng/mL, respectively) at all test points.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

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

		to vehicle. - Difference in proportion of eyes with complete resolution of anterior chamber cells (grade = 0) at Day 8 maintained through Day 15 - Difference in proportion of eyes with complete resolution of ocular pain (grade = 0) at Day 8 maintained through Day 15	double masked, parallel group study of 2 concentrations and dosing regimens of KPI-121 vs. vehicle	Vehicle B BID	121 1% 259 Vehicle	≥18 years who had undergone routine cataract surgery	

5.2 Review Strategy

The safety and efficacy of INVELTYS (loteprednol etabonate ophthalmic suspension, 1%) dosed BID for the proposed indication was based on the review of 2 randomized, double-masked, vehicle-controlled studies (Studies KPI-121-C-001 and -005) pivotal studies. Description of the trial design for the studies is included in section 5.3.

5.3 Discussion of Individual Studies/Clinical Trials

Studies KPI-121-C-001 and -005 were 2 multi-centered, randomized, double-masked, placebo controlled trials in which patients with an anterior cell grade greater than or equal to "2" (a cell count of 6 or higher using a slit-lamp biomicroscope) after cataract surgery were assigned to INVELTYS or placebo (vehicle) following surgery. One to two drops of INVELTYS or vehicle was self-administered twice a day for 14 days, beginning the day after surgery. Complete resolution of inflammation (a cell count of 0 maintained through day 15 without rescue medication) and complete resolution of pain (a patient-reported pain grade of 0 maintained through day 15 without rescue medication) was assessed 4, 8, and 15 days post-surgery.

6 REVIEW OF EFFICACY

6.1 Indication

Treatment of post-operative pain and inflammation following ocular surgery

6.1.1 Methods

The description of the clinical trial design is contained in Section 5.3.

The 2 studies (KPI-121-C-001 and -005) had similar inclusion and exclusion criteria and similar study populations were enrolled in each trial. Across the two trials, 900 subjects were enrolled and included in the

ITT populations. Of these, 515 subjects were randomized to the drug treatment group and 385 subjects were randomized to vehicle.

Inclusion/Exclusion Criteria

The study populations in Trials KPI-121-C-001 and KPI-121-C-005 comprised male and female subjects at least 18 years of age who were candidates for routine, uncomplicated cataract surgery, and who had potential post-operative Snellen Distance visual acuity by pinhole method of at least 20/200 in the study eye (in the opinion of the investigator).

To qualify for randomization at post-operative Day 1, a subject must have undergone routine, uncomplicated cataract surgery (e.g., phacoemulsification with posterior chamber intra-ocular lens implantation, not combined with any other surgery) and have ≥ Grade 2 anterior chamber cells (i.e., ≥ 6 cells). Subjects must also have continued to meet inclusion/exclusion criteria with respect to current ocular and medical conditions and must not have taken medications prohibited by protocol.

List of Investigators for Study KPI-121-C-001 and Subjects Enrolled

Site No.	Investigator Name	Sub-Investigator(s) Name	Hospital/Institution Name and Address	N
101	Ranjan P. Malhotra, MD, FACS	Gregg J. Berdy, MD, FACS Robert C. Brusatti, OD Debi (Deborah) Gravemann, RN, CCRP Jill Montgomery	Ophthalmology Associates 12990 Manchester Road Suite 200 St. Louis, MO 63131	18
102	Robert DaVanzo, MD	Michael Emile Tepedino, MD James Zachary Forsey, MD Cynthia M. Wood Cherle E. Michaelis Rhonda Spach Ana Hild	1400 East Hartley Drive High Point, NC 27262	33
104	Alice Epitropoulos, MD	Tracy McClelland	Ophthalmic Surgeons & Consultants of Ohio 262 Neil Avenue, Suite 430 Columbus, OH 43215	11
105	Raymond Fong, MD	Jeffrey C. Paccione, MD Douglas B. Friedrich, MD Jason J. Chen, OD Jenny Karn Yat Yoong (Grace) Kok Kian Yek Kok Chun Sang Ip	Raymond Fong, MDPC 109 Lafayette Street, 4th floor New York, NY 10013	47

106	Joseph Gira, MD	Micheal Donahoe, MD Erin Sullivan, OD Michelle Derhelmer, MD Amy Young Stephanie Williams	Ophthalmology Consultants Ltd. 12990 Manchester Road Suite 201 St. Louis, MO 63131	11
107	Damien Goldberg, MD	Barry Wolstan, MD	Wolstan & Goldberg Eye Associates 23600 Telo Avenue Suite 100 Torrance, CA 90505	20
108	Paul J. Hartman, MD	Alan H. Gruber, MD Howard I. Schenker, MD Mindy VanVoorhis, CCRC Michelle Hurley, COA Rachel Rivera Michelle Ciecierega	Rochester Ophthalmological Group, PC 2100 South Clinton Avenue Rochester, NY 14618	7
109	Farrell Tyson, MD	Michael Tibbitts, MD Stewart Kaplan, OD Jennifer Frederick Kathleen Bellaire	Argus Research at Cape Coral Eye Center 4120 Del Prado Boulevard S Cape Coral, FL 33904	8
110	Douglas Lorenz, DO	Mark Stradling, DO Surjeet Singh, MD Rene Zamora, MD Darrick Neibaur, DO Vincent Gassen, OD Douglas Orton, OD Rajy Rouweyha, MD Kris Taylor, CCRC Kylee Taylor, CRC	Nevada Eye and Ear 2598 Windmill Parkway Henderson, NV 89074 Las Vegas Physicians Research Group 870 Seven Hills Drive Suite 201 Henderson, NV 89052 Seven Hills Surgical Center 876 Seven Hills Drive Henderson, NV 89052 Stone Creek Surgical Center 5915 S. Rainbow Boulevard Las Vegas, NV 89118	4

111	Joseph Martel, MD	James Martel, MD Anna Chepurny Diana Chepurny Inna Topal Svetlana Brazhnikova Snow Hu Yee Lee Delores Figueroa	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670 Martel Eye Institute, LLC 11216 Trinity River Drive Rancho Cordova, CA 95670 Mercy San Juan Surgery Center 6660 Coyle Avenue Carmichael, CA 95608	30
112	Bernard Milstein, MD	Da-Thuy Van, DO Justin Irick, COA Loretta Driscoll, LVN Rebecca Rieck, COA Chance Caddell	The Eye Clinic of Texas, Affiliate of Houston, Eye Associates 1100 Gulf Freeway, Suite 114 League City, TX 77573 Area Surgicare Center 502 Medical Center Boulevard Webster, TX 77598	36
113	Sebastian Mora, MD	John Kozlovsky, MD Patricia Martinez Griselda Rodriguez Sandra Owens Jeannie Camacho, OD	Kozlovsky Delay & Winter Eye Consultants, LLC 2929 Mossrock, Suite 104 San Antonio, TX 78230	13
114	Michael Nordland, MD, PhD	Tracy Cruz Jen Bradford	Cincinnati Eye Institute 1945 CEI Drive Cincinnati, OH 45242 Cincinnati Eye Institute 4701 Central Avenue Middletown, OH 45044	45
115	Francis Price, MD	Yuri McKee, MD Mathew Feng, MD Kathleen Kelley, OD Faye Peters, OD Clorissa Quillin Tiffany Schendel Megan McDonald	Price Vision Group 9002 North Meridian Street Suite 100 Indianapolis, IN 46260	2

116	Charles Reilly, MD	William Flynn, MD Edward Rashid, MD Robert Rice, MD Catherine Flynn Hazen Anita Holland Suzanne DeLaCruz	R and R Eye Research, LLC 5430 Fredericksburg Road Suite 100 San Antonio, TX 78229 Specialty Surgery Center 5255 Prue Road Suite 100 San Antonio, TX 78240	19
117	Lawrence Roel, MD	Meredith Savage Lori Blackwell Tanya Dukes Richard M. Francis, MD	Westside Research, LLC 1413 John B White Sr. Boulevard Spartanburg, SC 29306	16
118	Kenneth Sall, MD	Leticia Guzman Clsneros, CCRC Cindy Lee, CCRC Ilanie Marie Shiell, CCRA Patricia Manjarrez, CCRC	11423 187th Street Suite 200 Artesia CA, 90701	16
119	John Sheppard, MD	Walter O Whitley, OD Elizabeth Yeu Lin, MD Dayna Lago, MD Stephen Scoper, MD	241 Coporate Boulevard Norfo k, VA, 23502	2
120	Robert J. Smyth-Medina, MD	Steven Rauchman, MD Joanne Perry Rosio Mendoza Rocio Rodriguez	11550 Indian Hills Road Suite 341 Mission Hills, CA, 91345	10
121	Joseph Tauber, MD	NA	Tauber Eye Center 4400 Broadway Suite 202 Kansas City, MO 64111	8
122	Lloyd Taustine, MD	Gregory M Su kowski, MD Brian K Kritchman, MD James D Hurt, OD Bridget Adkins, MBA Ashley Griffith, BS Amee Pierce, AS	1169 Eastern Parkway Suite 3427 Louisville, KY, 40217	6
123	Navin Tekwani, MD	Lisa Dinsmore Sarah Crocker Lisa Shepp	9911 Kennerly Road Suite A St. Louis, MO, 63128	15
125	Steve Wilson, OD	Timothy Schmitt, MD Liana Davis, LPN Paige Bunch, COA Latisha Briles Margaret Trimble, COA	519 State Street New A bany, IN, 47150	2

List of Investigators for Study KPI-121-C-005 and Subjects Enrolled

Site No.	Investigator Name	Sub-Investigator(s) Name	Hospital/Institution Name and Address	N
111	Joseph R. Martel, MD	James Benjamin Martel, MD, MPH Martha Orozco Cortes Unsa Anwar Nastya Padure	Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA,95670	44
118	Kenneth Sall, MD	Julie Kim, OD Jade Davis, OD Leticia Guzman, CCRC Cindy Lee, CCRC Patricia Manjarrez, CCRC Ilanie Shiell, CCRC	Sall Research Medical Center 11423 187th Street Suite 200 Artesia, CA 90701	15
131	Michael Korenfeld, MD	Nathan Tuttle, OD Janet Renee Zeitzmann, RN Michelle M. Mueller	Comprehensive Eye Care, Ltd. 901 East Third Street Washington, MO 63090 Mercy Hospital 901 East Fifth Street Washington, MO 63090	17
138	Jack Abrams, MD	Tapan R. Shah, MD Lindsey B. Kowal Beth Kimball, RN	Abrams Eye Institute 6450 Medical Center Street Suite 100 Las Vegas, NV 89148 Valley View Surgery Center 1330 S. Valley View Boulevard Las Vegas, NV 89102	6
140	Louis M. Alpern, MD	Terri Cintron	The Cataract and Glaucoma Center 4171 N. Mesa Building D100 El Paso, TX 79902	13
141	Jason Bacharach, MD	Lisa Teel, OD Angela Lewis Reynolds Celeste Campbell Maria Suarez Rebecca Craig	North Bay Eye Associates 104 Lynch Creek Way Suite 12 Petaluma, CA 94954 North Bay Eye Associates, Inc. Ambulatory Surgery Center 380 Tesconi Court Santa Rosa, CA 95401	12

142	Mark T. Bergmann, MD	Daniel J. Hammer, MD Barbara B. Henry, CCRC Natalie Carpenter	Apex Eye 6507 Harrison Avenue. Suite E Cincinnati, OH 45247 Trihealth Surgery Center 3660 Edgewood Drive Cincinnati, OH 45211 Mercy Health West Hospital 3300 Mercy Health Boulevard Cincinnati. OH 45211	20
143	James Boyce, MD	Norman Liu, MD Ryan Taban, MD Gladys Sager CCRC	Orange County Ophthalmology 12665 Garden Grove Boulevard, Suite 401 Garden Grove, CA 92843	30
145	David L. Cooke, MD	David N. Brown, MD Ronald L. McKey, MD Stanley W. Pletcher, MD Duane A. Tolsma, OD James Duryee Jennifer Adams Jennifer Zech	Great Lakes Eye Care 2848 Niles Road Saint Joseph, MI 49085 Great Lakes Eye Care 120 Longmeadow Village Drive Niles, MI 49120 Lakeland Center for Outpatient Services 3900 Hollywood Road Saint Joseph, MI 49085	19
146	Michael Depenbusch, MD	Erin Burk Mallory Barker Jerry Tolle, Jr. Kaitlin Isaacson Tricha Botchway Siedah Campbell Guadalupe Robles Maria Gonzalez Anita Schadlu, MD Ramin Schadlu, MD Shabari Seetharam, MD	Arizona Eye Center 604 W. Warner Road, Suite B6 Chandler, AZ 85225 Warner Park Surgery Center 604 W. Warner Road Building A Chandler, AZ 85225 Scottsdale Eye Institute 215 S. Power Road Suite 112 Mesa, AZ 85206 Desert Ridge Outpatient Surgery Center 20940 N. Tatum Boulevard # 100 Phoenix, AZ 85050	20

147	Sherif M. El-Harazi, MD	Kay Park, MD	Lugene Eye Institute 1510 South Central Avenue, Suite 300 Glendale, CA 91204	17
148	Robert H. Gross, MD	Jung T. Dao, MD Brandon K. Suedekum, MD Julie Komer Kristine Zakrzewski	Cornea and Cataract Consultants of Arizona 3815 E. Bell Road Suite 2500 Phoenix, AZ 85032	31
149	Preeya Gupta, MD	Terry Kim, MD Melissa Daluvoy, MD Gargi Vora, MD Robin R. Vann, MD	Duke University Duke Eye Center 2351 Erwin Road Durham, NC 27710 Duke Eye Center 4709 Creekstone Drive Durham, NC 27703	1
150	David Hardten, MD	Ahmad Fahmy, OD Christine Larson, MD Elizabeth Davis, MD Gina Doeden, OD Johnna Hobbs, OD Mona Fahmy, OD Mark Bubolz, OD Scott Hauswirth, OD Thomas Samuelson, MD Alicia Alvarado, OD	Minnesota Eye Consultants, PA 9801 Dupont Avenue S. Suite 200 Bloomington, MN 55431	6
151	Mitchell A. Jackson, MD	Heidi Spaw Maggie Sawa	Jackson Eye, S.C. 300 N. Milwaukee Avenue Lake Villa, IL 60046 Lindenhurst Surgery Center 1050 Red Oak Lane Lindenhurst, IL 60046	5
152	Brennan P. Greene, MD	John C. Meyer, MD Kellye Johnson Mandy Kessinger Angela Warfield Guruprasad R. Pattar, MD, PhD	The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	25
153	Karl Olsen, MD	Courtney Moon COA CCRC Marti Jo Chavez, BS, COA Kent Basford, DO Randall Smith, MD Linda Tews Brittney A belo	Eye Center of Northern Colorado, PC 1725 East Prospect Road Fort Collins, CO 80525	12

154	Richard J. Ou, MD	John M. Lim, MD Caroline Beard, CRC Santa Montelongo, CRC Stephanie Verkin, CRC Gihan Romany, CRC Bhavna Shah, CRC Connie Arredonde Naina Sudarshan	Houston Eye Associates 915 Gessner #250 Professional building 3 Houston, TX 77024 Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	8
155	James H. Peace, MD	Shohreh Neshat Daisy Hernandez Feliks Sinyak Arnold Penarroyo Carmelina Marin Rania Bara	United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301 Olympia Medical Center 5900 West Olympic Boulevard Los Angeles, CA 90036	19
156	Harvey J. Reiser, MD	Carrie A. Cardillo, OD Patti J. Myers, COT Christen Hogan, COA Patty Yuhas, COA	Eye Care Specialists 703 Rutter Avenue Kingston, PA 18704 Surgical Specialty Center of Northeastern Pennsylvania 190 Welles Street Forty Fort, PA 18704	20
157	Philip Lee Shettle, DO	None	Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	8
158	Bruce E. Silverstein, MD	Christopher Lin, MD Robert G. Trent, MD Bryan G. Crum, MD Mel Harris Kelly Miller Sandy Kelly	Shasta Eye Medical Group, Inc. 3190 Churn Creek Road Redding, CA 96002 Shasta Eye Medical Group, Inc. 900 Butte Street Redding CA 96001 Surgery Center of Northern California 950 Butte Street Redding CA 96001	30
159	Steven E. Smith, MD	Angela Kaplan, OD Ginger Marinell Monica Rumble	Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901 University Eye Surgery Center 13051 University Drive Fort Myers, FL 33907	9

161	Thomas Richard Walters, MD	Robert Edward Marquis, MD Yen Dang Nieman, MD Robert Stapper Cindy Jasek Elaine Marcin Kristin Mika Tracey Knox	Texan Eye, PA/Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731 Texan Eye, PA 7000 North Mopac Expressway Suite 110 and Suite165 Austin, TX 78731 Texan Surgery Center 7000 North Mopac Expressway Suite 120 Austin, TX 78731	21
162	Jon-Marc Weston, MD, FACS	Gregory M. Valle, OD Steven F. Tronnes, OD Jenna Bates Deborah M. Harding, COT Shantelle Weakley, CCRC, COA	Roseburg Research Associates, LLC 2435 NW Kline Street Roseburg, OR 97471 Vision Surgery & Laser Center, PC 2435 NW Kline Street Roseburg, OR 97471	7
173	Robert B. Pendleton, MD	Victor Wechter, MD Debbie McCluskey Diana Amador Yadira Topping Ivette Corona	Pendleton Eye Center 3637 Vista Way Oceanside, CA 92056 North Coast Surgery Center 3903 Waring Road Oceanside, CA 92056	16
186	John F. Kozlovsky, MD	Jeannine E. Camacho, OD Richard L. Delay, OD	Kozlovsky Delay & Winter Eye Consultants, LLC 2929 Mossrock, Suite 104 San Antonio, TX 78230 American Surgery Center 7810 Louis Pasteur Drive, Suite 100 San Antonio, TX 78229	2

187	Parag Majmudar, MD	Maria Rosselson, MD Tiffany Andrzejewski, OD Charles Faron, OD	Chicago Cornea Consultants 1585 N. Barrington Road Suite 502 Hoffman Estates, IL 60169 St Alexius Medical Center 1555 N. Barrington Road Hoffman Estates, IL 60169 Hoffman Estates Surgery Center 1555 N. Barrington Road, Suite 400 Hoffman Estates, IL 60169	6
206	Jeffrey Raymond Lozier, MD	Karen Mossbarger, CRC Nancy Burnham, COT, OSA Lynette Phifer, COA Ruth Bangs, Pam Emery, CCRC, CPT1 Marisol Perez	Arch Health Partners 15611 Pomerado Road 4th Floor Poway, CA 92064	18
243	Kerry D. Solomon, MD	Jeffery F. Hood, OD Helga P Sandoval, MD, MSCR Krissa L. Drentlaw, COT	Carolina Eye Care Physicians, LLC 1101 Clarity Road Suite 100 Mt. Pleasant, SC 29464 The Physicians' Eye Surgery Center 2060 Charlie Hall Boulevard Suite 301 Charleston, SC 29464	2
244	David Tyler Vroman, MD	Millin Chandu Budev, MD Michelle See Yuen Ying, MD Kristina D. Neff, MD Margaret E. Bozic, CCRC	Carolina Cataract & Laser Center 137 Gateway Drive Ladson, SC 29456 Physicians Eye Surgery Center 2060 Charlie Hall Boulevard Suite 301 Charleston, SC 29414	5
245	Don J. Perez-Ortiz, MD	Bernard R. Perez, MD	International Research Center 4506 Wishart Place Tampa, FL 33603	14
247	Thomas LoBue, MD	Ryan Miller, OD	LoBue Laser and Eye Medical Center 40700 California Oaks Road Suite 106 Murrieta, CA 92562	13

248	Frank Wilson McDonald, MD	Jeffery Levenson, MD Curtis Schmidt, OD Vontrece Williams	Levenson Eye Associates 751 Oak Street, Suite 200 Jacksonville, FL 32204 Riverside Park Surgicenter 2001 College Street Jacksonville, FL 32204	19
249	Robert C. Sorenson, MD, PhD	Barratt L. Philips, MD Roger Duncan Johnson, MD John Grant Tew, MD	Inland Eye Specialist 3953 W. Stetson Avenue Hemet, CA 92545	10

Reviewer's comments:

No individual site enrolled a disproportionate number of subjects in either clinical trial.

6.1.2 Demographics

KPI-121-C-001 and -005

For the pooled population, no important differences were observed between treatment groups for any of the demographic characteristics (i.e., age, sex, and race). 56.7% and 57.8% of subjects were female in the KPI-121 1% BID and vehicle BID groups, respectively. The mean age was 67.7 (range 38 to 89) in the KPI-121 1% BID group and 69.3 (range 40 to 90) in the vehicle BID group.

Demographics and Baseline Characteristics for Phase 3 Trials of Post-Operative Inflammation and Pain Following Ocular Surgery for the 1% BID dose

	KPI-121 1% BID (N=386)	**Vehicle BID (N=325)**
Age (years)		
n	386	325
Mean	67.7	69.3
SD	8.90	8.34
Min, Max	38, 89	40, 90
Gender, n (%)		
Male	167 (43.3)	137 (42.2)
Female	219 (56.7)	188 (57.8)
Ethnicity, n (%)		
Hispanic/Latino	52 (13.5)	44 (13.5)
Not Hispanic/Latino	334 (86.5)	281 (86.5)
Race, n (%)		
White	297 (76.9)	252 (77.5)

	KPI-121 1% BID (N=386)	Vehicle BID (N=325)
Asian	36 (9.3)	29 (8.9)
Black/African-American	36 (9.3)	34 (10.5)
Other Race	8 (2.1)	6 (1.8)
Native Hawaiian/Other Pacific Islander	4 (1.0)	2 (0.6)
Unknown	2 (0.5)	1 (0.3)
Mixed	2 (0.5)	0
American Indian/Alaskan Native	1 (0.3)	1 (0.3)

6.1.3 Subject Disposition

The median duration of exposure to study treatment was 14.0 days for subjects in the drug 1% BID, vehicle BID, and vehicle QID groups, and 15.0 days for subjects in the drug 0.25% QID group.

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

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

a The AE leading to withdrawal was eye pain.

6.1.4 Analysis of Primary Endpoint(s)

The between-group differences comparing KPI-121 1% were statistically significant favoring KPI-121 1% over vehicle for both primary endpoints in both trials KPI-121-C-001 and KPI-121-C-005.

Primary Efficacy Results for KPI-121 1% and Vehicle Groups in Trial KPI-121-C-001

	KPI-121 1% BID (N=125)	Vehicle[a] (N=126)	Between-Group Difference for % Responders[b] (95% CI)	p-value
Complete Resolution (Grade 0) of Anterior Chamber Cells at Day 8 and Maintained Through Day 15 with no Rescue Medication Prior to Day 15, n (%)	39 (31.2)	19 (15.1)	16.1 (5.9, 26.4)	0.0024
Complete Resolution (Grade 0) of Ocular Pain at Day 8 and Maintained Through Day 15 with no Rescue Medication Prior to Day 15, n (%)	67 (53.6)	43 (34.1)	19.5 (7.4, 31.5)	0.0019

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

Reviewer's comments:

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

Primary Efficacy Results for KPI-121 1% and Vehicle Groups in Trial KPI-121-C-005

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

Reviewer's comments:

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

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

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

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

Both clinical trials demonstrated statistically significant endpoints for inflammation and pain at p < 0.05 or better.

6.1.5 Analysis of Secondary Endpoints(s)

Key Non-Primary Efficacy Results in Trial KPI-121-C-001

	KPI-121 1% BID (N=125)	Vehicle[a] (N=126)	p-value
Complete Resolution of Ocular Pain at Day 4 Maintained Through Day 15 With No Rescue Medication Prior to Day 15, n (%)	55 (44.0)	32 (25.4)	0.0020
Complete Resolution of Anterior Chamber Cells at Day 15 With No Rescue Medication Prior to Day 15[b], n (%)	68(54.4)	38(30.2)	0.0001
Complete Resolution of Ocular Pain at Day 15 With No Rescue Medication Prior to Day 15[b], n (%)	89 (71.2)	60 (47.6)	0.0001

Key Non-Primary Efficacy Results in Trial KPI-121-C-005

	KPI-121 1% BID (N=261)	Vehicle BID (N=259)	p-value
Complete Resolution of Ocular Pain at Day 4 Maintained Through Day 15 With No Rescue Medication Prior to Day 15, n (%)	109 (41.8)	64 (24.7)	<0.0001
Complete Resolution of Anterior Chamber Cells at Day 15 With No Rescue Medication Prior to Day 15[a], n (%)	125 (47.9)	64 (24.7)	<0.0001
Complete Resolution of Ocular Pain at Day 15 With No Rescue Medication Prior to Day 15[a], n (%)	179 (68.6)	126 (48.6)	<0.0001

Reviewer's comments:

In both Phase 3 trials, the drug KPI-121 1% was consistently demonstrated to be superior to vehicle for the key secondary endpoints.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Evaluations of primary efficacy endpoints were conducted in subgroups defined by gender (male, female) and age group (< 69 years, ≥ 69 years) in each pivotal trial, separately. There was no evidence of any relevant differences in efficacy by age group or gender. In each subgroup, as evaluated in both trials, greater proportions of subjects in the KPI-121 1% group than in the vehicle group achieved the primary efficacy endpoints of complete resolution of anterior chamber cells and complete resolution of ocular pain.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosage and administration of KPI-121 proposed in this NDA for the treatment of post- operative inflammation and pain following ocular surgery is: KPI-121 1% applied as 1 to 2 drops to the affected eye BID for 2 weeks after surgery.

This dosing recommendation is based on the clinical safety and efficacy data derived from Trials KPI-121-C-001 and KPI-121-C-005, and supported by nonclinical data relative to the ocular pharmacokinetics of KPI-121.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 REVIEW OF SAFETY

Safety Summary

7.1 Methods

The safety profile of KPI-121 1% for the proposed indication is based on data derived from two phase 3 Trials KPI-121-C-001 and KPI-121-C-005. Safety assessments in these trials were: evaluation of AEs, Snellen distance visual acuity (VA) by pinhole method, slit-lamp biomicroscopy (palpebral conjunctival erythema, corneal edema, hyphema, ciliary flush, and bulbar conjunctival injection), IOP measurement, dilated ophthalmoscopy, and use of rescue medication.

Each pivotal trial included a 2-week treatment period and a follow-up visit that occurred 2 to 4 days following the end of treatment. AEs were collected for the entire study period, with no designation of “treatment period AEs” or “posttreatment-period AEs.” Because the target indication is for short term (i.e., 2 weeks) use, no evaluations of long-term safety were conducted.

The key design elements of Trial KPI-121-C-005 were identical to those of Trial KPI-121-C-001, except that eligible subjects were randomized to 1 of the following 2 study treatment arms in an approximate 1:1 ratio:

- KPI-121 1% BID
- Vehicle BID

A total of 520 subjects were randomized at 35 centers located in the US.

Trial KPI-121-C-001: Study Eye Adverse Events Reported by > 1% of Subjects in Any Treatment Group (Safety Population)

Overall Preferred Term	**KPI-121 0.25% QID (N=129)**	**KPI-121 1% BID (N=125)**	**Vehicle[a] (N=126)**
Number (%) of Subjects Reporting Any Study Eye AEs[b]	13 (10.1)	7 (5.6)	21 (16.7)
Corneal oedema	2 (1.6)	2 (1.6)	2 (1.6)
Eye pain	2 (1.6)	1 (0.8)	5 (4.0)
Photophobia	3 (2.3)	1 (0.8)	3 (2.4)
Punctate keratitis	3 (2.3)	1 (0.8)	0
Eye inflammation	2 (1.6)	0	4 (3.2)
Eye irritation	1 (0.8)	0	3 (2.4)
Ocular discomfort	0	0	2 (1.6)
Ocular hyperaemia	0	0	5 (4.0)

AE = adverse event; BID = twice daily; QID = four times daily
Note: At each level of summarization, subjects reporting more than one event are only counted once. Preferred terms (PTs) are presented by descending incidence in the KPI-121 1% BID group. AEs were coded using MedDRA version 16.1.
[a] In Trial KPI-121-C-001, the 2 vehicle groups (Vehicle A [QID] and Vehicle B [BID]) were pooled for all analyses.
[b] The numbers and percentages for overall AEs are inclusive of all PTs. PTs are only included in the table if >1% ofsubjects in any treatment group reported that AE.

Trial KPI-121-C-005: All Adverse Events Reported by >1% of Subjects in Any Treatment Group, by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	**KPI-121 1% BID (N=261)**	**Vehicle (N=259)**
Number (%) of Subjects Reporting Any AEs[a]	38 (14.6)	42 (16.2)
Eye disorders[a]	18 (6.9)	27 (10.4)
Cystoid macular oedema	3 (1.1)	3 (1.2)
Eye pain	3 (1.1)	6 (2.3)
Posterior capsule opacification[b]	3 (1.1)	4 (1.5)
Photophobia	1 (0.4)	4 (1.5)
General disorders and administration site conditions[a]	2 (0.8)	4 (1.5)
Instillation site pain	1 (0.4)	3 (1.2)
Infections and infestations[a]	9 (3.4)	3 (1.2)
Nasopharyngitis	4 (1.5)	1 (0.4)
Nervous system disorders[a]	5 (1.9)	6 (2.3)
Headache	4 (1.5)	4 (1.5)

AE = adverse event; BID = twice daily
Note: At each level of summarization, subjects reporting more than one event are only counted once. Within each system organ class (SOC), preferred terms (PTs) are presented by descending incidence in the KPI-121 1% BID group. AEs were coded using MedDRA version 16.1.
a The numbers and percentages for overall AEs and AEs by SOC are inclusive of all PTs. PTs are only included in the table if >1% of subjects in any treatment group reported that AE.
b The verbatim investigator term "posterior capsular opacity" reported in the study eye of an aphakic subject in the KPI-121 1% group should have coded to the MedDRA preferred term "posterior capsule opacification" and was mistakenly coded to "lenticular opacities" instead. Thus, the incidence of posterior capsule opacification in the KPI-121 1% group was 4/261 (1.5%) and there were 0 AEs of lenticular opacities.

Reviewer's comments:

No individual site enrolled a majority of subjects that would drive the overall results of the clinical trials.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 7.1.

7.1.2 Categorization of Adverse Events

MedDRA nomenclature was used to code adverse events. The number and percent of patients reporting adverse events was tabulated based on the system organ class and preferred term. Summary table were generated for all adverse events regardless of causality as well as for treatment-related adverse events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Refer to Section 7.1.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the 2 Phase 3 trials conducted in subjects with post-operative ocular inflammation and pain, 900 subjects were enrolled, received at least 1 dose of study treatment, and were included in the safety populations. Of these 900 subjects, 386 subjects were treated with KPI-121 1% BID, 129 subjects were treated with KPI-121 0.25% QID, 325 subjects were treated with vehicle BID, and 60 subjects were treated with vehicle QID. The majority (≥ 98.6%) of subjects completed the trial according to the respective protocol. A total of 1.4% (13/900) of subjects discontinued early, primarily due to withdrawal by subject or other reason.

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

	KPI-121 1% BID (N = 386)	KPI-121 0.25% QID (N = 129)	Vehicle BID (N = 325)	Vehicle QID (N = 60)	Overall (N = 900)
Completed Trial	382 (99.0%)	127 (98.4%)	319 (98.2%)	59 (98.3%)	887 (98.6%)
Subjects Withdrawn Early from the Trial	4 (1.0%)	2 (1.6%)	6 (1.8%)	1 (1.7%)	13 (1.4%)
Reason for Early Withdrawal					
Withdrawal by subject	1 (0.3%)	2 (1.6%)	5 (1.5%)	0	8 (0.9%)

Adverse event[a]	1 (0.3%)	0	0	0	1 (0.1%)
Lost to follow-up	0	0	1 (0.3%)	0	1 (0.1%)
Physician decision	0	0	0	1 (1.7%)	1 (0.1%)
Pregnancy	0	0	0	0	0
Other	2 (0.5%)	0	0	0	2 (0.2%)

Extent of Exposure

The median duration of exposure to study treatment was 14.0 days for subjects in the KPI-121 1% BID, vehicle BID, and vehicle QID groups, and 15.0 days for subjects in the KPI-121 0.25% QID group.

7.2.2 Explorations for Dose Response

Refer to Section 6.1.8.

7.2.3 Special Animal and/or In Vitro Testing

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

7.2.4 Routine Clinical Testing

The Clinical trials evaluated 2 active doses of KPI-121 (1% BID and 0.25% QID) for the treatment of post-operative pain and inflammation following ocular surgery.

7.2.5 Metabolic, Clearance, and Interaction Workup

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when INVELTYS is administered to a nursing woman.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

INVELTYS, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

Overall, most AEs were mild to moderate in severity. AEs were reported as severe for 1.0% (4/386) of subjects in the KPI-121 1% BID group and 2.2% (7/325) in the vehicle BID group. Severe AEs in the KPI-121 1% BID group included cholecystitis, eye pain, and pneumonia. Severe AEs in the vehicle BID group included abdominal pain, cerebrovascular accident, cholelithiasis, cystoid macular edema, eye inflammation, eye pain, hepatobiliary disorders, photophobia, and vomiting.

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

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

7.3.3 Dropouts and/or Discontinuations

Number (%) of Subjects Reporting Adverse Events Leading to Permanent Withdrawal of Study Treatment (Integrated Safety Population, Trials KPI-121-C-001 and KPI-121-C-005)

System Organ Class Preferred Term	KPI-121 1% BID (N = 386)	Vehicle BID (N = 325)
Number (%) of Subjects Reporting Any AE Leading to Permanent Withdrawal of Study Treatment	7 (1.8)	17 (5.2)
Eye Disorders	5 (1.3)	13 (4.0)
Corneal Oedema	2 (0.5)	4 (1.2)
Eye Pain	1 (0.3)	3 (0.9)
Macular Oedema	1 (0.3)	0
Photophobia	1 (0.3)	3 (0.9)
Ocular Hyperaemia	0	2 (0.6)
Anterior Chamber Fibrin	0	1 (0.3)
Eye Inflammation	0	1 (0.3)
Eyelid Oedema	0	1 (0.3)
Ocular Discomfort	0	1 (0.3)
Uveitis	0	1 (0.3)
Nervous System Disorders	1 (0.3)	3 (0.9)
Headache	1 (0.3)	2 (0.6)
Cerebrovascular Accident	0	1 (0.3)
Immune System Disorders	0	1 (0.3)
Hypersensitivity	0	1 (0.3)
Investigations	1 (0.3)	0
Intraocular Pressure Increased	1 (0.3)	0

In the KPI-121 1% BID and vehicle BID groups of the pivotal trials, AEs leading to permanent withdrawal of study treatment were reported for 1.8% (7/386) and 5.2% (17/325) of subjects. The AEs leading to permanent withdrawal of subjects in the KPI-121 1% BID group were corneal edema (2 subjects), eye pain, photophobia, macular edema, headache, and intraocular pressure increased (1 subject each). Of these, intraocular pressure increased was the only AE in the KPI-121 1% BID group to be considered by the investigator as treatment related. AEs leading to permanent withdrawal in the vehicle BID group were corneal edema (4 subjects), eye pain, photophobia (3 subjects each), ocular hyperemia, headache (2 subjects each), eye inflammation, anterior chamber fibrin, eyelid edema, ocular discomfort, uveitis, cerebrovascular accident, and hypersensitivity (1 subject each).

7.3.4 Significant Adverse Events

Adverse events related to dropouts/discontinuations are presented in Section 7.3.3. There were no other significant adverse events identified.

7.3.5 Submission Specific Primary Safety Concerns

There are no specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

AEs were reported by 13.7% (53/386) and 17.5% (57/325) of subjects in the KPI-121 1% BID and vehicle BID groups, respectively. No single preferred term was reported by > 1.6% of subjects in the KPI-121 1% BID group.

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

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

AE = adverse event; BID = twice daily
a The numbers and percentages for overall AEs and AEs by SOC are inclusive of all PTs. PTs are only included in the table if >2% of subjects in any treatment group reported that AE.
Note: at each level of summarization, subjects reporting more than one event are only counted once. AEs coded using MedDRA Version 16.1. Only the integrated data from the KPI-121 1% BID and Vehicle BID groups are presented in-text; additional data are available in the source table.

Reviewer's comments:

The risk of adverse events was low with eye pain and posterior capsule opacification occurring at 1% and headache at 1.6% in the KPI-121 1% drug group.

7.4.2 Laboratory Findings

Trial KPI-121-C-008 was conducted to assess systemic pharmacokinetics and safety of KPI-121 1% applied as 2 drops BID in 1 eye (per randomization) for 15 days (morning dose only on Day 15) in healthy adult subjects. Plasma samples were collected at various times after the first dose, prior to dosing on Day 8, and prior to and at various times following the last administered dose on Day 15. Pharmacokinetic evaluations were planned for loteprednol etabonate (LE) and its 2 major, inactive metabolites, PJ-90 and PJ-91. The lower limits of quantitation (LLOQ) for the assays were 1 ng/mL for LE and PJ-91 and 5 ng/mL for PJ-90.

In this trial, all plasma samples were below the LLOQ for evaluation of LE, PJ-90, and PJ-91, indicating undetectable (<1 ng/mL) systemic absorption of LE occurs with KPI-121 1% ophthalmic suspension, using the proposed dosing regimen of 1 to 2 drops BID for 14 days.

7.4.3 Vital Signs

No additional safety studies were conducted to address a specific safety concern as all plasma levels were below LLOQ (7.4.2).

7.4.4 Electrocardiograms (ECGs)

No additional safety studies were conducted to address a specific safety concern as all plasma levels were below LLOQ (Section 7.4.2).

7.4.5 Special Safety Studies/Clinical Trials

No additional safety studies were conducted to address a specific safety concern as all plasma levels were below LLOQ (Section 7.4.2).

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the integrated Safety population, the incidence of AEs was low and comparable across the 2 dose groups during the entire study.

7.5.2 Time Dependency for Adverse Events

No time dependency was noted for AEs in the clinical trials as expected due to the short period of treatment.

7.5.3 Drug-Demographic Interactions

The assessment of the AEs reported during trials of KPI-121 1% showed no evidence of any clinically relevant differences by gender or age group.

7.5.4 Drug-Disease Interactions

INVELTYS, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

7.5.5 Drug-Drug Interactions

This is minimal systemic exposure after administration; therefore, it is not expected that any drug-drug interaction would occur.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well controlled studies in pregnant women. Treatment of pregnant rats and rabbits with oral Loteprednol etabonate at doses above clinically relevant doses did produce teratogenic effects.

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when INVELTYS™ is administered to a nursing woman.

7.6.3 Pediatrics and Assessment of Effects on Growth

This application did not trigger PREA.

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

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

KPI-121 is non-narcotic and does not have abuse potential. It has not been shown to have sedative or abnormal cognitive effects and is therefore not expected to affect the ability to drive or operate machinery, or to impair mental ability.

7.7 Additional Submissions / Safety Issues

The 120 Safety Update was submitted on March 30, 2018.

In early 2018, Kala Pharmaceuticals, Inc. completed 2 clinical trials of KPI-121 0.25% ophthalmic suspension in the short-term relief of the signs and symptoms of dry eye disease. Trials KPI-121-C-006 and KPI-121-C-007 were multicenter, double-masked, randomized, vehicle-controlled, parallel-group, Phase 3 trials, which were designed to evaluate the efficacy and safety of KPI-121 0.25% ophthalmic suspension in approximately 900 subjects (per trial) with dry eye disease.

Summary of Adverse Event Reporting in Phase 3 Dry Eye Trials (Safety Populations)

	KPI-121-C-006		KPI-121-C-007	
	KPI-121 0.25% QID (N = 459)	Vehicle (N = 456)	KPI-121 0.25% QID (N = 452)	Vehicle (N = 453)
Number (%) of Subjects Reporting AEs	66 (14.4%)	62 (13.6%)	58 (12.8%)	44 (9.7%)
Number of AEs Reported	137	147	120	103

Reviewer's comments:

There was a low overall incidence of AEs reported during both trials and in both treatment groups with the results being unchanged for trials with KPI-121.

8 POSTMARKET EXPERIENCE

KPI-121 1% has not been marketed in any foreign country.

9.0 Appendices

None.

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

See labeling recommendations to the package insert attached at the end of this review.

9.3 Advisory Committee Meeting

Not required.

9.3 Clinical Investigator Financial Disclosure Review Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: 210565

Submission Date(s): October 24, 2017

Applicant: Kala Pharmaceuticals, Inc.

Product: Loteprednol etabonate ophthalmic suspension, 1%

Reviewer: Martin P Nevitt, M.D., M.P.H.

Date of Review: May 25, 2017

Covered Clinical Study (Name and/or Number): KPI-121-C-001 and KPI-121-C-005.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 58		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from

		applicant)

(b) (6)

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

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

/s/

MARTIN P NEVITT
08/03/2018

WILLIAM M BOYD
08/03/2018