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APPLICATION NUMBER:

208219Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208219
Priority or Standard	Standard
Submit Date(s)	April 25, 2018
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Division / Office	DTOP/OAP
Reviewer Name(s)	Martin P Nevitt, M.D., M.P.H.
Review Completion Date	January 16, 2019
Established Name	Loteprednol etabonate ophthalmic gel, 0.38%
(Proposed) Trade Name	Lotemax SM
Therapeutic Class	Corticosteroid
Applicant	Bausch Health Inc.
Formulation(s)	Topical ophthalmic gel
Dosing Regimen	Apply one drop into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period
Indication(s)	Treatment of postoperative inflammation and pain following ocular surgery
Intended Population(s)	Patients undergoing ocular surgery

Template Version: March 6, 2009

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% is recommended to be approved for the treatment of postoperative inflammation and pain following ocular surgery.

1.2 Risk Benefit Assessment

Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% is recommended for the treatment of postoperative inflammation and pain following ocular surgery based on two adequate and well controlled clinical trials.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Post-Marketing Requirements or Commitments.

2 Introduction and Regulatory Background

Loteprednol etabonate (LE) is a corticosteroid that was originally developed as a topical ophthalmic suspension 0.5% (Lotemax). Lotemax is approved for the treatment of steroid responsive inflammatory conditions ocular inflammatory disorders when the inherent hazard of steroid use is accepted to obtain an advisable diminution of edema and inflammation and treatment of postoperative inflammation following ocular surgery. Alrex (loteprednol etabonate ophthalmic suspension) 0.2% is approved for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis. A fixed combination product consisting of LE 0.5%/tobramycin 0.3% ophthalmic suspension (Zylet) is approved for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. LE ointment 0.5% (Lotemax) is approved for the treatment of post-operative inflammation and pain following ocular surgery.

LE ophthalmic gel 0.5% (LE Gel) for the treatment of post-operative inflammation and pain following ocular surgery was approved on September 28, 2012. The objective of a gel formulation was to provide an alternative ophthalmic delivery dosage form for patients requiring treatment for inflammation and pain following ocular surgery.

On July 20, 2018, NDA 202872 S-002 Lotemax (loteprednol etabonate ophthalmic gel) 0.5% was approved to treat post-operative inflammation following ocular surgery for childhood cataract in pediatric patients under the age of 12 years. There were no new safety concerns raised in this supplemental application concerning the use of LE ophthalmic gel 0.5% to treat post-operative inflammation following ocular surgery for childhood cataract in pediatric patients under the age of 12 years.

The applicant in support of the development program in this submission is cross referencing NDA 202872 which it owns.

2.1 Product Information

Established Name:	loteprednol etabonate ophthalmic gel, 0.38%
Proposed Trade Name:	Lotemax SM
Chemical Class:	gel formulation
Pharmacological Class:	corticosteroid
Indication	treatment of post-operative inflammation and pain following ocular surgery
Dosing Regimen:	Apply one drop into the conjunctival sac of the affected eye three times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period

2.2 Tables of Currently Available Treatments for Proposed Indication

Name of Drug	**Indication**
Vexol	Treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
Durezol	Treatment of inflammation and pain following ocular surgery.
Lotemax Ointment	Treatment of post-operative inflammation and pain following ocular surgery
Lotemax Suspension	Treatment of post-operative inflammation and pain following ocular surgery
Lotemax Gel	Treatment of post-operative inflammation and pain following ocular surgery

2.3 Availability of Proposed Active Ingredient in the United States

Loteprednol etabonate has been marketed in the US since 1998 as Lotemax and Alrex ophthalmic suspension drug products, since 2005 in a fixed combination with

tobramycin as Zylet, since 2011 as Lotemax ophthalmic ointment and since 2012 as Lotemax ophthalmic gel.

Drug	NDA	Indication
Lotemax (loteprednol etabonate ophthalmic suspension) 0.5%	20-583	Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, SPK, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. It is also indicated for the treatment of post-operative inflammation following ocular surgery.
Alrex (loteprednol etabonate ophthalmic suspension) 0.2%	20-803	Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.
Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) 0.5%/0.3%	50-804	Treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.
Lotemax (loteprednol etabonate ophthalmic ointment) 0.5%	200-738	Treatment of post-operative inflammation and pain following ocular surgery
Lotemax (loteprednol etabonate ophthalmic gel, 0.5%)	202872	Treatment of post-operative inflammation and pain following ocular surgery

2.4 Important Safety Issues With Consideration to Related Drugs

Lotemax is a topical corticosteroid. Ocular AEs generally associated with ophthalmic steroids include elevated IOP (which may be associated with optic nerve damage and visual acuity and field defects), posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Other reactions include acute anterior uveitis, keratitis, conjunctivitis, corneal ulcers, mydriasis, conjunctival hyperemia, and ptosis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The product development of loteprednol etabonate ophthalmic gel, 0.38% was conducted under IND 102654.

On June 10, 2013, an End-of-Phase 2 meeting was held to discuss the proposed development program for loteprednol etabonate ophthalmic gel, 0.38%.

On January 30, 2018, a Pre-NDA was held to discuss the application submission plan. At this meeting the Agency discussed the requirements for a PREA study and would consider NDA 202872 S-002 currently under review in lieu of a pediatric post marketing requirement. Subsequently, NDA 202872 S-002 was approved on July 10, 2018. The applicant requested a full waiver from conducting a PREA study for loteprednol etabonate ophthalmic gel, 0.38%; however since the current application is a reformulation of loteprednol and not a new active ingredient, new dosage form, new dosing regimen or new route of administration, PREA does not apply.

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 applicant.

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

Investigator / Sub-investigator	Site	Eyes Enrolled in Study 842	Eyes Enrolled in Study 875
(b) (6)			Not in study
			Not in study
			Not in study

Reviewer's comments:

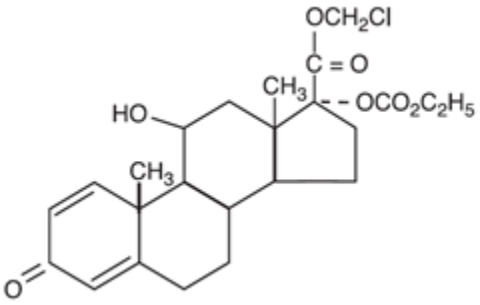
To prevent bias, Study 842 was a masked and randomized clinical trial with 514 total eyes enrolled. These sites listed in the table above only enrolled a total of (b) (6) eyes (b) (6) % of eyes enrolled); too few to influence the overall clinical results. See Appendix 9.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38% contains a sterile, topical corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



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

Chemical Name:
chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each gram contains:
Active: Loteprednol Etabonate 3.8 mg (0.38%)

Inactives: Boric acid, edetate disodium dihydrate, glycerin, hypromellose, poloxamer, polycarbophil, propylene glycol, sodium chloride, water for injection, and sodium hydroxide to adjust to a pH of between 6 and 7.

Preservative Added: Benzalkonium chloride 0.003%

Table 2.3.P.1–1 Qualitative and quantitative composition of LE 0.38% gel

Component[1]	Reference to Quality Standard	Function	Label strength: 0.38%	
			Amount (mg/g fill)	%(w/w)
Loteprednol etabonate, (b) (4)	In-house	Active ingredient	(b) (4)	0.38%
Glycerin	USP/ Ph.Eur.	(b) (4)		
Propylene glycol	USP/ Ph.Eur.			
Sodium chloride	USP/ Ph.Eur.			

Benzalkonium chloride	NF/ Ph.Eur.	Anti-microbial agent	0.003%
Polycarbophil	USP		
Hypromellose	USP		
Sodium hydroxide	NF/ Ph.Eur.	Alkalizing agent	
Poloxamer 407	NF		
Edetate disodium dihydrate	USP/NF		
Boric acid	NF/ Ph.Eur.		
Water for injection	USP/ Ph.Eur.		
		Total	-

1 The quantities of inactive ingredient in the formulation do not exceed the FDA's IID limit for the route of administration.

USP = United States Pharmacopeia; Ph.Eur.= European Pharmacopoeia; NF = National Formulary

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

Loteprednol etabonate was embryotoxic and teratogenic in rats and rabbits when administered orally during the period of organogenesis. Structural abnormalities in rat fetuses were observed at maternally toxic doses and included absent innominate artery, cleft palate and umbilical hernia. In rabbit fetuses, anomalies included meningocele, abnormal left common carotid artery, and limb flexures. No developmental effects were observed in rats or rabbits at 4 and 7 times the maximum daily clinical dose, respectively.

Loteprednol etabonate decreased offspring viability and development when dosed orally to pregnant rats from the beginning of organogenesis through the end of lactation at a maternally toxic dose. No adverse effects were observed in pregnant/lactating rats or in their offspring at a lower dose 6 times the maximum daily clinical dose.

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 tk assay, or in the chromosomal aberration test in human lymphocytes, or in vivo in the 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, (350 and 175 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

These findings are consistent with the findings in other corticosteroids when dosed to non-human animals.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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

4.4.3 Pharmacokinetics

Measurable concentrations of loteprednol etabonate were observed in plasma after topical ocular administration of a single dose and 2 weeks of three times daily dosing of Lotemax SM. Systemic exposure to loteprednol etabonate is low (i.e., <0.20 ng/mL) following either single dose or daily bilateral administration with minimal increase in systemic loteprednol etabonate exposure after 2 weeks of three times daily dosing. Mean Cmax values for loteprednol etabonate in plasma were 0.133 ng/mL and 0.160 ng/mL after a single administration and on Day 15, respectively. The mean AUC0-t values for loteprednol etabonate in plasma were 0.148 hr•ng/mL and 0.353 hr•ng/mL after a single administration and on Day 15 after 2 weeks of three times daily dosing, respectively.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Number of Subjects	Diagnosis of Patients	Duration of Treatment
Study 842	Efficacy and Safety of LE GEL 0.38% versus vehicle in the treatment of inflammation and pain	Prospective, multi-center, randomized, double masked, placebo controlled LE GEL 0.38% - BID and TID - Topical ocular	514 eyes randomized (171 LE BID, 171 LE TID, 172 vehicle)	Male and female subjects with specified amount of anterior chamber cells following routine uncomplicated cataract surgery	14 Days

	following cataract surgery				
Study 875	Efficacy and Safety of LE GEL 0.38% versus vehicle in the treatment of inflammation and pain following cataract surgery	Prospective, multi-center, randomized, double masked, placebo controlled LE GEL 0.38% - BID and TID - Topical ocular	600 eyes randomized (201 LE BID, 200 LE TID, 199 vehicle)	Male and female subjects with specified amount of anterior chamber cells following routine uncomplicated cataract surgery	14 Days
Study 843	Efficacy and Safety of LE GEL 0.38% versus vehicle in the treatment of inflammation and pain following cataract surgery	Prospective, multi-center, randomized, double masked, placebo controlled LE GEL 0.38% - BID - Topical ocular	326 eyes randomized (163 LE BID, 163 vehicle)	Male and female subjects with specified amount of anterior chamber cells following routine uncomplicated cataract surgery	14 Days

5.2 Review Strategy

The source of clinical data utilized in this review include the study listed in section 5.1.

5.3 Discussion of Individual Studies/Clinical Trials

Studies 842 and 875

Studies 842 and 875 had similar clinical designs.

Title: Multi-Center, Double-Masked, Vehicle-Controlled, Randomized, Parallel-Group Study to Assess Loteprednol Etabonate Ophthalmic Gel, 0.38% (BID and TID) versus Vehicle Gel for the Treatment of Ocular Inflammation and Pain Following Cataract Surgery

Study Design

Subjects were randomized to receive LE gel 0.38% or vehicle, BID or TID, for the management of postoperative inflammation and pain following routine, uncomplicated cataract surgery. Subjects were randomized in a 2:2:1:1 ratio to LE gel 0.38% BID, LE gel 0.38% TID, vehicle BID, and vehicle TID. The 2 vehicle arms were combined into 1

treatment group in the statistical analysis, and hence the study had 3 treatment groups: LE gel 0.38% BID, LE gel 0.38% TID, and combined vehicle group.

Eligible subjects who were enrolled in the study were seen for 7 scheduled study visits over the course of approximately 4 weeks. Treatment duration for this study was approximately 14 days. Visit 1 was the Screening Visit and occurred up to 14 days prior to surgery. Visit 2 was the day of surgery. At Visit 3 (Postoperative Day 1), eligibility for randomization into the study was assessed. If eligible, subjects were randomized and completed postoperative study Visits 4, 5, 6, and 7 (Postoperative Days 3, 8, 15, and 18, respectively).

The initial dose of study drug occurred in the clinic at Visit 3 (Postoperative Day 1). Subjects randomized to BID groups instilled 1 drop of study drug into the study eye, 2 times per day at approximately 12-hour intervals. Subjects randomized to TID groups instilled 1 drop of study drug into the study eye, 3 times per day at approximately 8-hour intervals. Study treatment lasted approximately 14 days, with the last dose administered on the evening before Visit 6 (Postoperative Day 15).

Grading Scales Used for Studies 842 and 875

Anterior Chamber Cells:

Assess accumulation of white blood cells in aqueous. Pigment cells and red blood cells were to be ignored. Assess anterior chamber using a high-power field slit beam of 1 mm x 1 mm.

0 = No cells seen

1 = 1 - 5 cells

2 = 6 - 15 cells

3 = 16 - 30 cells

4 = >30 cells

Pain in the Study Eye:

Ocular pain, defined as a positive sensation of the eye, including foreign body sensation, stabbing, throbbing, or aching, was assessed and graded by subjects on the 6-point scale below:

0 =	None:	Absence of positive sensation.
1 =	Minimal:	Presence of mild sensation or discomfort typical of postoperative ocular surgery (eg, diffuse or focal foreign body sensation, mild transient burning or stinging, etc.)
2 =	Mild:	Mild, tolerable aching of the eye.
3 =	Moderate:	Moderate aching sufficient to require the use of over-the-counter (OTC) acetaminophen.
4 =	Moderately Severe:	More prolonged aching requiring the use of an OTC analgesic other than acetaminophen.

Schedule of Visits

PROCEDURE/ASSESSMENT[a]	Visit 1 Screening	Visit 2 Surgery[b]	Visit 3 Postop Day 1[c]	Visit 4 Postop Day 3 (±1 Day)	Visit 5 Postop Day 8 (±1 Day)	Visit 6 Postop Day 15 (±1 Day)	Visit 7 Postop Day 18 (±1 Day)	Early Discontinuation
Informed Consent and HIPAA authorisation	X							
Urine Pregnancy Test, as applicable	X		X				X	X
Demographics	X							
Current and Relevant Medical/Ophthalmic History	X							
Ocular Symptoms	X		X	X	X	X	X	X
Study Drug Sensation Assessment					X			
Pin-holed Snellen VA	X		X	X	X	X	X	X
Slit Lamp Biomicroscopy	X		X	X	X	X	X	X
IOP Examination (Goldman applanation tonometry)[d]	X		X	X	X	X	X	X
Dilated Fundus Examination	X					X		X
Determine Eligibility	X		X					
Dispense Study Drug[e]			X[f]					
AEs[g] and Concomitant Medications	X	X	X	X	X	X	X	X
Collect Study Drug[e]						X		X
Dispense and Collect Study Diary			X[h]	X[i]	X[i]	X[i, j]		X[i, j]
Exit Study							X	X

Abbreviations: AC = anterior chamber; AE = adverse event; HIPAA = Health Insurance Portability and Accountability Act; IOP = intraocular pressure; Postop = postoperative; VA = visual acuity.

[a] All ophthalmic assessments were performed bilaterally.
[b] Visit 2 occurred within 14 days of Visit 1. Screening and surgery could not take place on the same day.
[c] Visit 3 occurred 18 to 34 hours post-surgery. During this visit, subject eligibility was confirmed based on AC cell assessment.
[d] IOP was assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening).
[e] Study drug dispensation and collection were performed by the unmasked designee.
[f] Subjects instilled initial dose while in clinic. The Investigator was not allowed to be present for the in-office instillation. Study treatment lasted approximately 14 days with the last dose administered on the evening before Visit 6.
[g] Collection of AEs extended from the time the subject gave informed consent until the last study visit.
[h] Dispensed only.
[i] Diary cards were checked for accuracy and compliance.
[j] Collected only.

Inclusion Criteria

A subject was eligible for enrollment if ALL of the following criteria applied:

Visit 1 (Screening) Criteria

1. Was 18 years or older on the date the ICF was signed and with the capacity to provide voluntary informed consent.
2. Able to read, understand, and provide written informed consent on the IRB/EC approved ICF and provide HIPAA authorization.
3. Willing and able to comply with all treatment and follow-up/study procedures.
4. Was a candidate for routine, uncomplicated cataract surgery (phaco-emulsification with posterior chamber intraocular lens [IOL] implantation, not combined with any other surgery).
5. In the Investigator's opinion, had potential postoperative pin-holed Snellen visual acuity (VA) of at least 20/200 in the study eye at Visit 1 (Screening) and at least 20/200 in the fellow eye.
6. For female subjects, either
   - Not be of childbearing potential (female subjects not of childbearing potential must have been postmenopausal at least 12 months prior to Visit 3 or permanently sterilized [eg, tubal occlusion, hysterectomy, bilateral salpingectomy])

or

   - Had a negative urine pregnancy test result at Visit 1 (Screening).
7. For female subjects of child-bearing potential, or male subjects with partners of child bearing potential, agreed to use adequate contraceptive methods prior to and during the study treatment period, as described below.
   - Female subjects of childbearing potential must have used at least 1 form of the following acceptable contraceptive methods:
     - Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine device [IUDs]) at least 14 days prior to Visit 3 (the first dose of study drug)
     - True abstinence (when this was in line with the preferred and usual lifestyle of the subject)
     - Placement of a copper-containing IUD prior to Visit 3
     - Use of condoms with spermicidal foam/gel/film/cream/suppository at least 14 days prior to Visit 3
     - Male partner who had a vasectomy at least 3 months prior to Visit 3.
   - Male subjects with partners of childbearing potential must have used at least 1 form of the following acceptable contraceptive methods:
     - True abstinence (When this is in line with the preferred and usual lifestyle of the subject)
     - Vasectomy at least 3 months prior to Visit 3

- Without a vasectomy, must have used a condom with spermicidal foam/gel/film/ cream/suppository.

8. Willing to postpone cataract surgery on the fellow eye, if deemed necessary, until after study completion.

Visit 3 (Postoperative Day 1) Criteria

9. Underwent routine, uncomplicated cataract surgery (phaco-emulsification with posterior chamber IOL implantation, not combined with any other surgery) in the study eye.
10. For female subjects, either
    - Was not of childbearing potential (female subjects not of childbearing potential must have been postmenopausal at least 12 months prior to Visit 3 or permanently sterilized [eg, tubal occlusion, hysterectomy, bilateral salpingectomy])

or

    - Had a negative urine pregnancy test result at Visit 3 (Postoperative Day 1).
11. Continued to meet all requirements of Inclusion Criterion 7.
12. Had ≥ Grade 2 anterior chamber (AC) cells (6-15 cells) in the study eye.

Exclusion Criteria

A subject who met any of the following exclusion criteria was not to be enrolled:

1. Had a severe/serious ocular condition or history/presence of chronic generalized systemic disease that the Investigator felt might increase the risk to the subject or confound the result(s) of the study.
2. Was a female subject who was pregnant or breast feeding.
3. Had ocular hypertension (IOP ≥ 21 mmHg), glaucoma, or any glaucoma-related incisional or laser surgery in the study eye. Note: IOP criteria must have been met at both Visit 1 (Screening) and Visit 3 (Postoperative Day 1).
4. Was monocular (fellow eye was nonfunctional or fellow eye's pinhole vision was worse than Snellen 20/200).
5. Had ocular surgery (including laser surgery) in the study eye within 3 months or in the fellow eye within 2 weeks prior to Visit 1 (Screening).
6. Had a current diagnosis of cystoid macular oedema in the study eye.
7. Had any abnormality that prevented reliable Goldmann applanation tonometry in either eye.
8. Had iris atrophy in the operative eye.
9. Had lens pseudoexfoliation syndrome with glaucoma or zonular compromise in the study eye.
10. Was unable, for any reason, to discontinue contact lens use in the study eye during the course of the study.
11. Had a history of chronic or recurrent inflammatory eye disease in the study eye (eg, iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis, herpes simplex infection, etc.).

12. Had proliferative diabetic retinopathy or moderate to severe non-proliferative diabetic retinopathy in the study eye.
13. Had any intraocular inflammation in either eye (cells or flare score greater than Grade 0 at slit lamp examination) or ocular pain greater than Grade 1 in the study eye at Visit 1 (Screening).
14. Had a congenital ocular anomaly in either eye.
15. Had a presence of active external ocular disease: infection (bacterial, viral or fungal) or inflammation (including allergic) of the study eye.
16. Had used ocular therapy (either eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, antihistamines, or decongestants within 7 days prior to surgery or was expected to require any of these treatments during the 18 days following cataract surgery.
17. Was expected to require treatment with systemic NSAIDs, antihistamines, or decongestants during the 18 days following cataract surgery with the exception of ≤ 81 mg/day of acetylsalicylic acid.
18. Was expected to require treatment with any systemic, inhaled, nasal, or ocular (either eye) corticosteroids or glucocorticoids during the 18 days following cataract surgery or had used any systemic or ocular corticosteroids within 14 days prior to cataract surgery. Dermal use outside the ocular area was permitted.
19. Was expected to require concurrent systemic or ocular therapy with immunosuppressants (eg, Restasis®) during the 18 days following cataract surgery or had used ocular immunosuppressants within 30 days prior to surgery.
20. Had known hypersensitivity or contraindication to the study drug(s) or their components.
21. Had participated in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation, including use of an investigational intraocular lens in the study eye.
22. Had been previously randomized in this study.
23. Currently required or was expected to require treatment with any medication listed as a disallowed medication per the Disallowed Therapy Section of the protocol of the clinical study report [CSR]).

Primary Efficacy Variables:

The hierarchical primary efficacy endpoints were:

1. The proportion of subjects with complete resolution of AC cells (cell score = 0) in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle.
2. The proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle.

The secondary efficacy endpoints included:

- Proportion of subjects with complete resolution of AC cells in the study eye at each visit and for each subject's final on-treatment visit.

- Proportion of subjects with Grade 0 pain in the study eye at each visit and for each subject's final on-treatment visit.
- Proportion of subjects with complete resolution of AC flare in the study eye at each visit and for each subject's final on-treatment visit.
- Proportion of subjects with complete resolution of both AC cells and AC flare in the study eye at each visit and for each subject's final on-treatment visit.
- Change from baseline in AC cells and flare, combined and separately, at each follow-up visit. The combined endpoint (Anterior Chamber Reaction) was defined as the sum of the scores for AC cells and AC flare.
- Proportion of treatment failures at Visit 5 (Postoperative Day 8). A subject was considered a treatment failure at Visit 5 if they started any rescue medication prior to, or on the day of, Visit 5. If a subject did not have a Visit 5, due either to early discontinuation or to a missed visit, then treatment failure at Visit 5 was defined as starting rescue medication prior to, or on, Postoperative Day 9.

Study 842

*An asterisk indicates no subjects were enrolled at the site.

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
102	120814	Berdy, Gregg J., M.D.	Brusatti, Robert C., OD Gravemann, Debi, RN, CCRP Hayes, Bridget D., COT Malhotra, Ranjan P., M.D. Montgomery, Jill	Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	**Total: 13** LE gel 0.38% BID: 4 LE gel 0.38% TID: 5 Vehicle: 4
103	120329	Bergmann, Mark Thomas, M.D.	Bosse, Emily Henry, Barbara, B. Meier, Edward J., M.D.	Apex Eye 2859 Boudinot Ave., Suite 301 Cincinnati, OH 45238	**Total: 11** LE gel 0.38% BID: 4 LE gel 0.38% TID: 1 Vehicle: 6
104	861293	Branch, James, M.D.	Acosta, Elaine, COA Revis, Catherine, COA	James D. Branch, M.D. 224 Town Run Lane Winston-Salem, NC 27101	**Total: 33** LE gel 0.38% BID: 10 LE gel 0.38% TID: 13 Vehicle: 10
105	130506	Cooke, David L., M.D.	Adams, Jennifer L., COT Brown, David N., M.D. Cho, Sarah M., OD Duryee, James R., COT Herrman, Marilyn S., COA McKey, Ronald L., M.D. Pletcher, Stanley W., M.D. Tolsma, Duane A., OD Zech, Jennifer R.	Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085	**Total: 4** LE gel 0.38% BID: 2 LE gel 0.38% TID: 2 Vehicle: 0
150	130700	Crane, Charles J., M.D.	Krupa, Mary, Asst. Study Coordinator Vitale, Shirley, LPN, CRCST – Study Coordinator	Northern New Jersey Eye Institute 71 Second Street South Orange, NJ 07079	**Total: 1** LE gel 0.38% BID: 1 LE gel 0.38% TID: 0 Vehicle: 0
142	140827	Dehning, Doug O., M.D.	Chaney, Erika Dawson, Brett Thomas, OD Dresch, Brenda Duffett, Sheri Hasanin, Lisa Lewman, Ronia Nold, Christi Peola, Lisa Rosenthal, Judy Timbrook, Laura Wilson, Lindsey	Discover Vision Centers 4741 South Cochise Drive Independence, MO 64055	**Total: 4** LE gel 0.38% BID: 1 LE gel 0.38% TID: 3 Vehicle: 0
147	140069	Depenbusch, Michael J., M.D.	Bogner, Jaclyn Burk, Erin Campbell, Siedah Carpenter, Meaghan Qamar, Tariq, M.D.	Arizona Eye Center 604 W. Warner Road, Suite B-6 Chandler, AZ 85225	**Total: 8** LE gel 0.38% BID: 2 LE gel 0.38% TID: 2 Vehicle: 4
106	140150	Dunn, Steven H., M.D.	Arredondo, Connie Gray, Carole	Houston Eye Associates 915 Gessner, Suite 250 Houston, TX 77024	**Total: 1** LE gel 0.38% BID: 0 LE gel 0.38% TID: 1 Vehicle: 0
107*	150273	Elmer, Thomas R. Jr., M.D.	Edson, Erin C. Endl, Michael J., M.D. Fitche, Claus M., M.D. Goodnick, Kathleen, E. Grant, Linda S. Harpster, Patricia A. Hurley, Peter Emmett, M.D. Phillips, Pamela A. Riches, Gina	Fichte, Endl & Elmer Eye Care 2825 Niagara Falls Boulevard, Suite 130 Amherst, NY 14228	**Total: 0** LE gel 0.38% BID: 0 LE gel 0.38% TID: 0 Vehicle: 0

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
108	986169	Fishman, Arthur M., M.D.	Angel, Alejandro Suarez, COA Angella, Guy J., M.D. Disgdiertt, Alicia Stanbary, Easter, COT, CCRC	Eye Surgery Associates 603 North Flamingo Road, Suite 250 Pembroke Pines, FL 33028	**Total: 1** LE gel 0.38% BID: 0 LE gel 0.38% TID: 1 Vehicle: 0
109	160102	Fong, Raymond, M.D.	Friedrich, Douglas B., M.D. Kam, Jenny Kok, Yat Yoong (Grace) Kok, Kian Yek Yuen, Albert	Raymond Fong M.D., PC 109 Lafayette Street, 4th Floor New York, NY 10013	**Total: 48** LE gel 0.38% BID: 16 LE gel 0.38% TID: 16 Vehicle: 16
110	160465	Frenkel, Ronald E.P., M.D., FACS, FICS	Garthwaite, Carol A. Hesse, Edith (Sue), COT Punckowski, Laura R. Seith, Heather B. Stanton, Jade Woodlief, Norman F., M.D.	East Florida Eye Institute 509 SE Riverside Dr, Suite 302 Stuart, FL 34994	**Total: 9** LE gel 0.38% BID: 3 LE gel 0.38% TID: 2 Vehicle: 4
111	949206	Fried, Walter I., PhD, M.D.	Breigenzer, Wendy Castro, Joanne Huckeby, Becky Jacobs, Brian J., M.D. Randell, Amy Savitt, Michael Lee, M.D.	Walter I. Fried, M.D. 3477 Grand Avenue Gurnee, IL 60031	**Total: 2** LE gel 0.38% BID: 2 LE gel 0.38% TID: 0 Vehicle: 0
112	170002	Gira, Joseph P., M.D.	Amato, Josh Elliot, M.D. Caros, Jennifer Moellering, BA, MBA, CCRP Derheimer, Michelle R., OD Donahoe, Michael P., M.D. Krishnasamy, Senthil, M.D. Lee, Steven F., M.D. Sullivan, Erin Cleary, OD Young, Amy L.	Ophthalmology Consultants 12990 Manchester Road, Suite 201 St. Louis, MO 63131	**Total: 17** LE gel 0.38% BID: 6 LE gel 0.38% TID: 5 Vehicle: 6

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
113	453654	Graham, Michael P., M.D.	Carney, Billie, COA Jones, Teresa, COA	Magruder Eye Institute 1911 North Mills Avenue Orlando, FL 32803	**Total: 3** LE gel 0.38% BID: 2 LE gel 0.38% TID: 1 Vehicle: 0
124	170766	Greene, Brennan P., M.D.	Forward, Hope M. Meyer, John C., M.D.	The Eye Care Institute 1536 Story Ave Louisville, KY 40206	**Total: 13** LE gel 0.38% BID: 3 LE gel 0.38% TID: 3 Vehicle: 7
115*	200779	Johnson, C. Starck, M.D.	Palmer, Jennifer Rupp, Tara Salinas, Elizabeth Tubbs, Carl B., M.D.	Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134	**Total: 0** LE gel 0.38% BID: 0 LE gel 0.38% TID: 0 Vehicle: 0
116	200104	Jong, Kevin Y., M.D.	Beard, Caroline Sue Becho, Christine, COA Badillo, Marcella DelBosque, Norma A. Gamble, Zelisha Montelongo, Santa, CCRC Verkin, Stephanie, PA, CRC Villarreal, Veronica Zaman, Fiaz, M.D.	Houston Eye Associates 2855 Gramercy Street Houston, TX 77025	**Total: 22** LE gel 0.38% BID: 7 LE gel 0.38% TID: 6 Vehicle: 9
117	726415	Jorizzo, Paul Albert, M.D.	Jackson, Mindy Koenigsman, Helen, M.D. Oliva, Matthew S., M.D. Seney, Kristi Smith, Heather, CRC	Medical Eye Center 1333 E. Barnett Road Medford, OR 97504	**Total: 4** LE gel 0.38% BID: 1 LE gel 0.38% TID: 2 Vehicle: 1
118	504607	Katzman, Barry, M.D.	Delgado, Erika R. Nguyen, Quang Nhat, OD Patel, Gitane, M.D. Patel, Sarjan H., M.D. Roman, Pedro Daniel	West Coast Eye Care Associates 6945 El Cajon Boulevard San Diego, CA 92115	**Total: 6** LE gel 0.38% BID: 2 LE gel 0.38% TID: 1 Vehicle: 3

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
119	505606	Korenfeld, Michael S., M.D.	Mueller, Michelle M. Schmitz, Ashley, RN Tuttle, Nathan Mark, OD Zeitzmann, Janet Renee, RN	Comprehensive Eye Care, Ltd. 901 E. 3rd Street Washington, MO 63090	**Total: 6** LE gel 0.38% BID: 3 LE gel 0.38% TID: 2 Vehicle: 1
120	220105	Leonardo, Donna, DO	Matta, Noelle, CO, CRC, COT Pavlica, Michael R., M.D. Silbert, David Irving, M.D.	Family Eye Group 2110 Harrisburg Pike, Ste 215 Lancaster, PA 17601	**Total: 6** LE gel 0.38% BID: 2 LE gel 0.38% TID: 1 Vehicle: 3
121	220790	Liu, Norman H., M.D.	Boyce, James D., M.D., FACS Gasso, Ruth Pham, Jennifer	Orange County Ophthalmology Medical Group 12665 Garden Grove Blvd., Ste 401 Garden Grove, CA 92843	**Total: 21** LE gel 0.38% BID: 6 LE gel 0.38% TID: 6 Vehicle: 9
122	230039	Macaluso, Damien Charles, M.D.	Birt, Pamela Crandall, James David, M.D. Ferg, Marcie B., CRC Giberga, Jennifer Edmonds Haynes, William Lee, M.D. Isbey, Edward K., III, M.D., FACS Lane, Timothy	Asheville Eye Associates 8 Medical Park Drive Asheville, NC 28803	**Total: 4** LE gel 0.38% BID: 1 LE gel 0.38% TID: 1 Vehicle: 2
123	795351	Majmudar, Parag A., M.D.	Andrzejewski, Tiffany M., OD Faron, Charles A., OD Rosselson, Maria, M.D.	Chicago Cornea Consultants, Ltd. 1585 N. Barrington Road, Suite 502 Hoffman Estates, IL 60169	**Total: 4** LE gel 0.38% BID: 1 LE gel 0.38% TID: 1 Vehicle: 2
125	979176	Modi, Satish S., M.D. FRCS(C), CPI	D'Agostino, Sarah Mallozzi, Kelly Wolter, Andreas, M.D.	Alterman, Modi & Wolter 23 Davis Avenue Poughkeepsie, NY 12603	**Total: 4** LE gel 0.38% BID: 1 LE gel 0.38% TID: 3 Vehicle: 0

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
126	250328	Olsen, Karl, M.D.	Anderson, Heather Bashford, Kent P., DO Gardunio, Jacob Novacek, Terri D. Shachtman, William A., M.D. Smith, Randall W., M.D. Zeller, Patricia	Eye Center of Northern Colorado, P.C. 1725 East Prospect Road Fort Collins, CO 80525	**Total: 10** LE gel 0.38% BID: 3 LE gel 0.38% TID: 4 Vehicle: 3
127	859295	Peace, James H. M.D.	Bellemare, Lacie Marin, Carmelina Neshat, Shohreh M. Penarroyo, Arnold M.	United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	**Total: 12** LE gel 0.38% BID: 4 LE gel 0.38% TID: 3 Vehicle: 5
128	797349	Pendleton, Robert B., M.D., PhD.	Amador, Diana, COA Avila, Steven McCluskey, Debra Rizo, Jose Wechter, Victor, M.D.	Pendleton Eye Center 3637 Vista Way Oceanside, CA 92056	**Total: 22** LE gel 0.38% BID: 7 LE gel 0.38% TID: 11 Vehicle: 4
129	252853	Perez, Bernard R., M.D., FACS	Johnson, Rita Lara, Carlos Ortiz, Don J. Perez, M.D., FACS Pineiro, Jenny, CRC Whidden, Michelle, CRC	DBA International Research Center 4506 Wishart Place Tampa, FL 33603	**Total: 9** LE gel 0.38% BID: 2 LE gel 0.38% TID: 3 Vehicle: 4
130	650488	Peters, Newton Timothy, M.D.	Goldblatt, Warren, M.D. Haskell, Susan , OD Kallay, Sunny, CCRP Surette, Janea, COA Wood, Jill, BS	Eyesight Ophthalmic Services 19 Webb Place Dover, NH 03801	**Total: 7** LE gel 0.38% BID: 3 LE gel 0.38% TID: 3 Vehicle: 1

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
131	752391	Protzko, Eugene E., M.D.	Ahmed, Noushin Summit, OD Cranmer, Mallory A., OD Crespo, Christina M. Giordano, Candice R., M.D. Jantzi, Julianne Joy, OD Kershner, Nicole Amber, OD Makach, Tanya Marcinkiewicz, Pennylynn Nelson, Heidi Neutze-Heaney, Kimberly Ann, DO Reed, David D., OD Seidenberg, Carol Seidenberg, Jonathan A., M.D. Shastri, Neal K., OD Smearman, Scott M., OD	Seidenberg Protzko Eye Associates 2023 Pulaski Highway Havre De Grace, MD 21078	**Total: 9** LE gel 0.38% BID: 3 LE gel 0.38% TID: 2 Vehicle: 4
132	980175	Reiser, Harvey J., M.D.	Brady, Kaetlin Cardillo, Carrie A., OD Hogan, Christen McGraw, Joseph Patrick, M.D. Myers, Patti J. Roth, Richard E., DO Savage, Donald J., M.D. Yuhas, Patty	Eye Care Specialist 703 Rutter Avenue Kingston, PA 18704	**Total: 10** LE gel 0.38% BID: 3 LE gel 0.38% TID: 4 Vehicle: 3

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
133	280270	Rice, Robert A., M.D.	DeLaCruz, Suzanne Flynn, William John, M.D. Hazen, Catherine M. Flynn Holland, Anita, R. Ledesma, Natalie Rashid, Edward R., M.D. Reilly, Charles "Chaz", M.D. Saenz, Maria	R and R Eye Research, LLC 5430 Fredericksburg Road, Suite 100 San Antonio, TX 78229	**Total: 20** LE gel 0.38% BID: 6 LE gel 0.38% TID: 8 Vehicle: 6
134	280206	Ritterband, David C., M.D.	Fry, Kristen Lynne, OD Koplin, Richard Steven, M.D. Seedor, John Arthur, M.D.	Ophthalmic Consultants / New York Eye and Ear Infirmary 310 East 14th Street, 2nd Floor, South Building New York, NY 10003	**Total: 5** LE gel 0.38% BID: 2 LE gel 0.38% TID: 1 Vehicle: 2
148*	280072	Roel, Lawrence Edmund, M.D., PhD, FACS	Blackwell, Lori Dukes, Tanya Francis, Richard McMaster, Jr., M.D. Savage, Meredith L.	Westside Research, LLC 1413 John B. White Sr. Blvd, Suite G Spartanburg, SC 29306	**Total: 0** LE gel 0.38% BID: 0 LE gel 0.38% TID: 0 Vehicle: 0
135	290107	Shettle, Philip Lee, DO, FAOCO	Shettle, Debbie	Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	**Total: 11** LE gel 0.38% BID: 6 LE gel 0.38% TID: 5 Vehicle: 0
136	712429	Shulman, David G., M.D.	Lazar, Courtney E. Lazar-Svochak Deborah, COA, CCRC Lynn, Patricia, COA Trujillo, Fernando, M.D.	David G. Shulman, M.D., PA 999 E. Basse, Suite 127 San Antonio, TX 78209	**Total: 3** LE gel 0.38% BID: 1 LE gel 0.38% TID: 1 Vehicle: 1

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
137	863291	Silverstein, Bruce E., M.D.	Crum, Bryan Glenn, M.D. Grela, Courtney, CRC Hodges, Sheri L., CRC Kelly, Sandra (Sandy), CRC Lin, Christopher, M.D., FACS Miller, Kelly, BS Trent, Robert Grinnell, M.D.	Shasta Eye Medical Group, Inc 3190 Churn Creek Road Redding, CA 96002	**Total: 25** LE gel 0.38% BID: 7 LE gel 0.38% TID: 12 Vehicle: 6
138	490621	Silverstein, Steven M., M.D., FACS	Bentley, Cindy, BS, CRC Dominguez, Eddie Kleinsasser, Kelsey J., OD	Silverstein Eye Centers 4240 Blue Ridge Road, Suite 1000 Kansas City, MO 64133	**Total: 1** LE gel 0.38% BID: 0 LE gel 0.38% TID: 1 Vehicle: 0
139	836315	Smith, Stephen E., M.D.	Gribosky, Nancy Lighthall, Meghan J. Marinell, Ginger Verlaan, Coleen L., COT	Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	**Total: 12** LE gel 0.38% BID: 3 LE gel 0.38% TID: 4 Vehicle: 5
140	992163	Taustine, Lloyd R., M.D.	Adkins, Bridget Griffith, Ashley Hurt, James D., OD Kritchman, Brian K., M.D. Martin, Kimberly, COA Pierce, Amee Sulkowski, Gregory Michael, M.D.	Taustine Eye Center 1169 Eastern Parkway, Suite 3334 Louisville, KY 40217	**Total: 5** LE gel 0.38% BID: 2 LE gel 0.38% TID: 3 Vehicle: 0
141	591545	Tepedino, Michael Emile, M.D.	Da Vanzo, Robert John, M.D. Forsey, James Zachary, M.D. Michaelis, Cherie Eddinger, CCRC Shaw, Steven James, M.D. Spach, Rhonda Wood, Cynthia M., CCRA	Cornerstone Eye Care 307 N. Lindsay Street High Point, NC 27262	**Total: 26** LE gel 0.38% BID: 11 LE gel 0.38% TID: 4 Vehicle: 11

Site #	Investigator #	Principal Investigator	Sub-investigator(s)	Site Address	No. of Subjects Enrolled
149	130068	Toyos, Melissa Morrison, M.D.	Buchholz, Reyanna Mulliniks, Haylie Lynne, OD Toyos, Rolando, M.D.	Toyos Clinic 1800 State Street Nashville, TN 32703	**Total: 2** LE gel 0.38% BID: 0 LE gel 0.38% TID: 2 Vehicle: 0
143	976179	Tyson, Farrell C., II, M.D., FACS	Bellaire, Kathleen A. Frederick, Jennifer L. Gallo, Jennifer L. OD Kaplan, Stuart I., OD	Cape Coral Eye Center 4120 Del Prado Blvd. Cape Coral, FL 33904	**Total: 24** LE gel 0.38% BID: 6 LE gel 0.38% TID: 6 Vehicle: 12
146	140272	Van, Da-Thuy, DO	Driscoll, Loretta, LVN Irick, Justin, COA Milstein, Bernard A., M.D. Rieck, Rebecca	Texas Clinical Research Center 1100 Gulf Freeway, Suite 114 League City, TX 77573	**Total: 35** LE gel 0.38% BID: 13 LE gel 0.38% TID: 10 Vehicle: 12
144	978177	Walters, Thomas Richard, M.D.	Baley, Robert E., III Jasek, Cindy Lumby, Danielle Marcin, Elaine Marquis, Robert Edward, M.D. Mika, Kristin Stapper, Robert C.	Keystone Research (Texan Eye) 5717 Balcones Dr. Austin, TX 78731	**Total: 16** LE gel 0.38% BID: 7 LE gel 0.38% TID: 6 Vehicle: 3
145	330042	Wirta, David Louis, M.D.	Abbascia, Kimberly Abbascia, Yvette Kurteeva, Katerina, M.D. Porto, Jenny Tyner, Heather Wirta, Linda	David M. Wirta, M.D. 520 Superior Ave, Suite 235 Newport Beach, CA 92663	**Total: 5** LE gel 0.38% BID: 2 LE gel 0.38% TID: 0 Vehicle: 3

Study 875

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
001	210904	Kim, Janet Kiehong, M.D.	Sampson, Reginald, M.D.	Hull Eye Center 1739 W. Ave Lancaster, CA 93534	**Total: 28** Vehicle: 9 LE gel BID: 12 LE gel TID: 7
002	260921	Pai, Vicky Chia-Pei, M.D.	Savetsky, Michael Jeremy, M.D. Vu, Qui, M.D.	Mark B. Kislinger, MD, PhD, Inc. 210 South Grande Ave. Glendora, CA 91741	**Total: 2** Vehicle: 1 LE gel BID: 1 LE gel TID: 0
003	220806	LoBue, Thomas David, M.D.	None	LoBue Laser & Eye Medical, Inc. 40700 California Oaks Rd. Suite 106 Murrietta, CA 92562	**Total: 34** Vehicle: 17 LE gel BID: 8 LE gel TID: 9
004	290263	Segal, Zachary Kaufman, M.D.	Segal, Alan J., M.D., F.A.C.S	Med Eye Associates 5858 SW 68th St. Miami, FL 33143	**Total: 36** Vehicle: 15 LE gel BID: 14 LE gel TID: 7
005	765379	Tauber, Joseph, M.D.	Hefler, Megan, COA Kelley, Stephanie	Tauber Eye Center 4400 Broadway St.	**Total: 3** Vehicle: 2

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
				Suite 202 Kansas City, MO 64111	LE gel BID: 1 LE gel TID: 0
006	180092	Hovanesian, John Armen, M.D.	Lemieux, Leslie, Clinical Research Coordinator Raoof, Duna, M.D. Skvarna, Karen Phelps, D.O. Stefanidis, Nicoletta Jane, OD, FAAO	Harvard Eye Associates 24401 Calle De La Louisa Suite 300 Laguna Hills, CA 92653	**Total: 8** Vehicle: 3 LE gel BID: 2 LE gel TID: 3
007	290916	Sorenson, Robert Christian, M.D., PhD	Johnson, Roger Duncan, M.D. Phillips, Barratt Lee, M.D. Tew, John Grant, M.D.	Inland Eye Specialists 3953 W. Stetson Ave. Hemet, CA 92545	**Total: 10** Vehicle: 5 LE gel BID: 2 LE gel TID: 3
009	150036	El-Harazi, Sherif Mostafa, M.D., M.P.H.	Cruz, Claudia, Technician De La Cruz, Evelyn, CRC Garcia, Albert, Technician Morales, Adolfo, CRC Park, Kay Loren, M.D. Torres, Monica, CCRC	Lugene Eye Institute 1510 S. Central Ave. Suite 300 Glendale, CA 91204	**Total: 14** Vehicle: 2 LE gel BID: 6 LE gel TID: 6
011	320594	Vroman, David Tyler, M.D.	Bozic, Margaret E., CCRC	Carolina Cataract and Laser Center, LLC	**Total: 1** Vehicle: 1

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
			Budev, Millin Chandu, M.D. Neff, Kristiana D., M.D. Ying, Michelle See Yuen, M.D.	137 Gateway Dr. Ladson, SC 29456	LE gel BID: 0 LE gel TID: 0
013	290749	Stonecipher, Karl Gene, M.D.	Choi, Tony Tachwan, M.D.	Physicians Protocol/Laser Defined Vision 1002 N. Church St. Greensboro, NC 27401	**Total: 6** Vehicle: 1 LE gel BID: 4 LE gel TID: 1
014	240162	Nielsen, Steven	Esco, Ashlie Esco, Ryan A. Hoey, Helen Mannion, Sarah Moreira, Helen R., M.D. Pellegrino, Frank J. Wong, Pearl	Nielsen Eye Center 300 Congress St. Quincy, MA 02169	**Total: 27** Vehicle: 6 LE gel BID: 8 LE gel TID: 13
016	110895	Alpern, Louis M., M.D.	Cintron, Teresa, COA	The Cataract and Glaucoma Center 4171 North Mesa St. Building D, Suite 100 El Paso, TX 79902	**Total: 12** Vehicle: 2 LE gel BID: 5 LE gel TID: 5
017	581554	Macy, Jonathan Isaac, M.D.	None	Macy Eye Center 8635 W 3rd St.	**Total: 6** Vehicle: 2 LE gel BID: 3

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
				Suite 360W Los Angeles, CA 90048	LE gel TID: 1
018	150898	Epitropoulos, Alice T., M.D. FACS	Davis, Tracy J., COA, CRC Chambers, Megan Marie, M.D.	The Eye Center of Columbus 262 Neil Ave. Suite 430 Columbus, OH 43215	**Total: 9** Vehicle: 6 LE gel BID: 2 LE gel TID: 1
019	250204	Ou, Richard J., M.D.	Lim, John M., M.D.	Houston Eye Associates 915 Gessner Suite 250 Professional Building 3 Houston, TX 77024	**Total: 9** Vehicle: 5 LE gel BID: 2 LE gel TID: 2
020	220207	Logan, Andrew Gardner, M.D.	Clark, Tonika Concepcion, Ana Dunbar, Ruth Gonzalez, Tatnay Kelly, Natasha McCall, Christine Nguyen, Mindy Palmer, Strattene Redmond, Tara	Logan Ophthalmic Research, LLC 7401 N. University Dr. Suite 201 Tamarac, FL 33321	**Total: 24** Vehicle: 6 LE gel BID: 5 LE gel TID: 13
021	110895	Gollamudi, Subba Rao, M.D.	McQuirter, Henry G., O.D. Sanford, Michael Stephens, Tawnee	Eye Specialty Group 825 Ridge Lake Blvd. Memphis, TN 38120	**Total: 7** Vehicle: 1 LE gel BID: 4 LE gel TID: 2

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
022	210903	Khachikian, Stephen Seth, M.D.	Spencer, Terrence S., M.D	Black Hills Regional Eye Institute 2800 Third St. Rapid City, SD 57701	**Total: 17** Vehicle: 2 LE gel BID: 6 LE gel TID: 9
024	665474	Malhotra, Ranjan P., M.D.	Berdy, Gregg J., M.D Brusatti, Robert C., O.D Gravemann, Debroah (Debi), RN, CRRP Royer, Andrew, O.D. Wiemers, Dawn, B.S., MBA	Ophthalmology Associates 12990 Manchester Rd. Suite 200 St. Louis, MO 63131	**Total: 12** Vehicle: 3 LE gel BID: 6 LE gel TID: 3
025	280910	Rashid, Edward Raymond, M.D., FACS	Flynn, William John, M.D. Hazen, Catherine Ortega, Lauren Rice, Robert Alan, M.D. Reilly, Charles Daniel, M.D. Rodriguez, Griselda Rodriguez, Tracy	R and R Eye Research, LLC 5430 Fredericksburg Rd Suite 100 San Antonio, TX 78229	**Total: 25** Vehicle: 9 LE gel BID: 8 LE gel TID: 8
027	781364	Schultze, Robert Lee, M.D. FACS	Abessi, Bryan, M.D. Cortese, Michael Joseph, O.D.	Cornea Consultants of Albany 9 Vista Rd. Slingerlands, NY 12159	**Total: 1** Vehicle: 0 LE gel BID: 1 LE gel TID: 0

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
			Eden, Robert Alexander, M.D. Grill, Jennifer Marie, O.D. FAAO Revai, Judy Park, O.D.		
028	722419	Dao, Jung T., M.D.	Gross, Robert H, M.D. Komer, Julie Suedekum, Brandon K., M.D. Zakrzewski, Kristine	Cornea and Cataract Consultants of Arizona 3815 East Bell Rd. Suite 2500 Phoenix, AZ 85032	**Total: 39** Vehicle: 13 LE gel BID: 11 LE gel TID: 15
031	290914	Sandor, Charles, S., M.D.	Andreoli, Barbara Jean, O.D. Sander, Linda H. Sacher, Bradley Adam, MD	Clinical Research Center of Wheaton Eye Clinic, LLC 2015 North Main St. Wheaton, IL 60187	**Total: 1** Vehicle: 0 LE gel BID: 1 LE gel TID: 1
033	220890	Levenson, Jeffrey, M.D.	McDonald, Frank, M.D. Schmidt, Curtis, O.D. Williams, Vontrece	Levenson Eye Associates 751 Oak St. Suite 200 Jacksonville, FL 32204	**Total: 35** Vehicle: 9 LE gel BID: 9 LE gel TID: 17
034	230702	Martel, Joseph Reuben, M.D.	Martel, James Benjamin, M.D. MPH, FACS	Martel Eye Medical Group 11216 Trinity River Dr. Rancho Cordova, CA 95670	**Total: 30** Vehicle: 14 LE gel BID: 10 LE gel TID: 6

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
036	330919	Wolter, Andreas	Lynch, Karen, COA Mallozzi, Kelly, COA Melendez, Tiffany, COA Modi, Satish S., M.D., FRCS, CPI Ortiz, Sarah, COA, CCRC	Alterman, Modi & Wolter 23 Davis Ave. Poughkeepsie, NY 12603	**Total: 4** Vehicle: 2 LE gel BID: 1 LE gel TID: 1
039	330918	Wellish, Kent Lewis, M.D.	Bernal, Elizabeth Cummings, Peggy Davis, Jasmine Holly, Miriam A. Ilardi, Jan Mattheis, Jay Kenneth C., M.D., MSPH, FACS McCandless, Kenneth C., O.D. Peterson, Michael Roach, Taniyah	Wellish Vision Institute 2110 East Flamingo Suite 210/211 Las Vegas, NV 89119	**Total: 25** Vehicle: 10 LE gel BID: 9 LE gel TID: 6
040	170899	Giordano, Candice Rovecamp. M.D.	Cantu, Emilie Crespo, Christina M. Neutze-Heaney, Kimberly Ann, D.O. Reed, David D., O.D. Seidenberg, Carol	Seidenberg Protzko Eye Associates 2023 Pulaski Highway Havre De Grace, MD 21078	**Total: 14** Vehicle: 8 LE gel BID: 2 LE gel TID: 4

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
			Smearman, Scott M. O.D.		
041	459650	Stewart, William Colby, M.D.	Shaikh, Adeel Hafeez, M.D.	Houston Eye Associates 1415 North Loop Suite 400 Houston, TX 77022	**Total: 25** Vehicle: 5 LE gel BID: 7 LE gel TID: 13
042	360131	Zaman, Fiaz, M.D.	Arnoult, Jeffrey B., M.D.	Houston Eye Associates – Zaman 2855 Gramercy St. Houston, TX 77025	**Total: 20** Vehicle: 9 LE gel BID: 9 LE gel TID: 2
048	130897	Corrales Regalado, Gustavo A., M.D.	Malik, Khurram J., M.D.	Emerson Clinical Research Institute 410 South Washington St. Falls Church, VA 22046	**Total: 9** Vehicle: 4 LE gel BID: 2 LE gel TID: 3
050	130896	Cooper, H. Douglas, M.D.	Lech, Aaron E., M.D. Wayne, Jeffrey D., M.D.	Clinical Trials Research 114 North Sunrise Ave. Suite C1, C2, C3 Roseville, CA 95661	**Total: 2** Vehicle: 0 LE gel BID: 1 LE gel TID: 1
051	270920	Qamar, Tariq Ud-Dean, M.D.	Barker, Mallory, M.S. Burk, Erin, M.S. Carpenter, Meaghan, B.S. Isaacson, Kaitlin, B.A. Rosenbush, Kaylee, MS Tolle Jr., Jerry	Q Vision 215 S. Power Rd. Suite 112 Mesa, AZ 85206	**Total: 15** Vehicle: 3 LE gel BID: 7 LE gel TID: 5

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
052	290923	Shah, Pankajkumar Gopaldas, M.D.	Alcantar, Salvador, O.D. Gomez, Maria R., COA, SC Guerra, Sandra	Shah Research, LLC 1506 E. Griffin Parkway Mission, TX 78572	**Total: 13** Vehicle: 6 LE gel BID: 4 LE gel TID: 3
054	290925	Shtein, Roni Mintz, M.D. M.S.	Bixler, Jill Elizabeth, M.D. Hood, Christopher Thomas, M.D. Shah, Manjool Manoj, M.D.	University of Michigan Kellogg Eye Center 1000 Wall St. Ann Arbor, MI 48105	**Total: 2** Vehicle: 0 LE gel BID: 1 LE gel TID: 1
055	330924	WuDunn, Darrell, M.D., Ph.D.	Evans, Joshua William, M.D.	Indiana University Dept. of Ophthalmology Eugene and Marilyn Glick Eye Institute 1160 W. Michigan St. Indianapolis, IN 46202	**Total: 1** Vehicle: 1 LE gel BID: 0 LE gel TID: 0
057	330513	Walline, Timothy Andrew, M.D.	Cassell, Michael A., M.D. Desai, Komal Bharat, M.D Krishna, Rohit, M.D. Macaluso, Katie J., M.D. Teresa Nolan Pikey, Kevin P., D.O. Poulose, Abraham K., M.D.	Sabates Eye Centers 11261 Nall Ave. Leawood, KS 66211	**Total: 1** Vehicle: 0 LE gel BID: 1 LE gel TID: 0

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
			Sabates, Nelson Raymond, M.D. Starr, Richard, B.A.		
058	130927	Chapman, Jack Mabry, M.D.	Blehm, Clayton Gregg, M.D. Reynolds, Tania Roxanne, COT Smith, Cindy A. Williams, Kim Marie, CST	Accusite Surgical Services Upstate Clinical Trials 2061 Beverly Rd. Gainesville, GA 30501	**Total: 2** Vehicle: 0 LE gel BID: 2 LE gel TID: 0
060	230929	Marefat, Babak, M.D.	Teeter, Scott, M., M.D.	Cotton-O'Neil Clinical Research Center 823 SW Mulvane St. Suite 220 Topeka, KS 66606	**Total: 5** Vehicle: 1 LE gel BID: 1 LE gel TID: 3
061	330930	Warner, Evan Jared, M.D.	Crosser, Vicki A., COA Moyes, Andrew L., M.D. Verachtert, Anthony J., O.D.	Moyes Eye Center 515 NW 88th St. Kansas City, MO 64154	**Total: 14** Vehicle: 4 LE gel BID: 3 LE gel TID: 7
064	330407	Walman, Gerald, B., M.D.	Barker, Mallory, M.S. Burk, Erin, M.S. Carpenter, Meaghan, B.S. Moriarty, Sean P., B.A., COA Rosenbush, Kaylee, MS	Walman Eye Center 10615 W. Thunderbird Blvd. Suite D180 Sun City, AZ 85351	**Total: 15** Vehicle: 5 LE gel BID: 6 LE gel TID: 4

Site #	Investigator #	Principal Investigator	Subinvestigator(s)	Site Address	No. of Subjects Enrolled
			Tolle Jr., Jerry		
065	150101	Endl, Michael John, M.D.	Elmer, Thomas Robert, Jr., M. D.D	Fichte, Endl & Elmer Eyecare 6500 Porter Rd. Suite 2020 Niagara Falls, NY 14304	**Total: 16** Vehicle: 2 LE gel BID: 6 LE gel TID: 8
067	130934	Clay, Emma Louise, M.D., FACS	Hartman, Carl Trevor, M.D. FACS Nhu, Thuc-Trinh Thi, M.D. FACS Pasquali, Theodore August, M.D.	Southern California Eye Physicians and Associates 3300 E.South St. Suite 105 Long Beach, CA 90805	**Total: 21** Vehicle: 5 LE gel BID: 9 LE gel TID: 7

Reviewer's comments:

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

6 Review of Efficacy

6.1 Indication

Lotemax SM (loteprednol etabonate ophthalmic gel), 0.38% is proposed to be indicated for the treatment of postoperative inflammation and pain following ocular surgery.

6.1.1 Methods

The three phase 3 studies were conducted with LE gel 0.38%, (Study 842, Study 843, and Study 875). Study 842 and Study 875 included BID and TID dosing groups, and Study 843 only included a BID dosing group. Otherwise, the three studies used nearly identical protocols; therefore, the three studies were pooled for evaluating the safety of LE gel, 0.38% with respect to the extent of exposure, analysis of adverse events, and observations related to ocular safety and tolerance.

Study 843 failed its primary endpoint. Study 843 tested BID dosing only compared to vehicle. The efficacy results were:

Study 843 Primary Efficacy Result of LE Gel, 0.38% Phase 3 Efficacy Trial

Study	Treatment Arms	No. Enrolled/ Completed per Arm	LE gel, 0.38% BID vs. Vehicle
843	LE Gel BID Vehicle	163/154 163/143	**Anterior Chamber Cells at Visit 5 (Postop Day 8)** LE Gel BID = 23.6% Vehicle= 17.8% Difference (95% CI) = 5.5% (-3.2%, 14.3%) P=0.2174
			Ocular Pain at Visit 5 (Postop Day 8) LE Gel BID = 73.6% Vehicle= 59.5% Difference (95% CI) = 14.1% (4.0%, 24.2%) P=0.0069

In Study 843, a total of 326 subjects were randomized (vehicle, 163 subjects; LE gel 0.38% BID, 163 subjects) and included in the analysis.

The proportion of subjects with complete resolution of anterior chamber cells was higher in the LE gel 0.38% BID group (23.3%) compared to the vehicle group (17.8%), but the difference was not statistically significant (Pearson Chi-squared test: p = 0.2174).

A nominally statistically significant greater proportion of subjects in the LE gel 0.38% BID group (73.6%) compared to the vehicle group (59.5%) had complete resolution of ocular pain at Visit 5 based on analysis performed with the prospectively-defined analysis population (i.e., ITT population with missing data imputed as treatment failures) (Pearson Chi-squared tests: p = 0.0069). However, the criteria for success were not fulfilled and the primary study endpoint was not met because statistical significance was not achieved for the first hierarchical endpoint (complete resolution of anterior chamber cells at Visit 5).

6.1.2 Demographics

Studies 842 and 875

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	**LE gel 0.38% BID (N=171)**	**LE gel 0.38% TID (N=171)**	**Vehicle BID & TID (N=199)**	**LE gel 0.38% BID (N=201)**	**LE gel 0.38% TID (N=200)**
Age (years)						
N	172	171	171	199	201	200
Mean (SD)	69.0 (8.56)	70.0 (8.34)	70.5 (8.15)	68.5 (8.92)	68.3 (9.11)	67.9 (9.32)

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	**LE gel 0.38% BID (N=171)**	**LE gel 0.38% TID (N=171)**	**Vehicle BID & TID (N=199)**	**LE gel 0.38% BID (N=201)**	**LE gel 0.38% TID (N=200)**
Median	70.0	70.0	71.0	68.0	69.0	69.0
Min, Max	42, 87	46, 96	43, 89	38, 88	42, 91	36, 92
Gender, n (%)						
Male	72 (41.9)	77 (45.0)	82 (48.0)	83 (41.7%)	84 (41.8%)	70 (35.0%)
Female	100 (58.1)	94 (55.0)	89 (52.0)	116 (58.3%)	117 (58.2%)	130 (65.0%)
Race, n (%)						
American Indian or Alaska Native	0	0	1 (0.6)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Asian	23 (13.4)	18 (10.5)	18 (10.5)	7 (3.5%)	13 (6.5%)	9 (4.5%)
Black or African American	24 (14.0)	22 (12.9)	22 (12.9)	14 (7.0%)	23 (11.4%)	23 (11.5%)
Native Hawaiian or Other Pacific Islander	2 (1.2)	0	1 (0.6)	0 (0.0%)	1 (0.5%)	0 (0.0%)
White	119 (69.2)	126 (73.7)	125 (73.1)	169 (84.9%)	158 (78.6%)	163 (81.5%)
Other	3 (1.7)	4 (2.3)	3 (1.8)	9 (4.5%)	4 (2.0%)	3 (1.5%)
Multiple Races Checked	1 (0.6)	1 (0.6)	1 (0.6)	0 (0.0%)	1 (0.5%)	1 (0.5%)
Iris Color – Study Eye, n (%)						
Blue	35 (20.3)	39 (22.8)	35 (20.5)	50 (25.1%)	47 (23.4%)	49 (24.5%)
Brown	106 (61.6)	100 (58.5)	102 (59.6)	111 (55.8%)	115 (57.2%)	112 (56.0%)
Green	11 (6.4)	8 (4.7)	10 (5.8)	17 (8.5%)	9 (4.5%)	5 (2.5%)
Hazel	20 (11.6)	23 (13.5)	23 (13.5)	20 (10.1%)	28 (13.9%)	32 (16.0%)
Other	0	1 (0.6)	1 (0.6)	1 (0.5%)	2 (1.0%)	2 (1.0%)

Abbreviations: LE, loteprednol etabonate ophthalmic gel; BID, two times a day; TID, three times a day; ITT, intent-to-treat; N, number of subjects per treatment group; n, number of subjects in a demographic category; SD, standard deviation; Min, minimum; Max, maximum
Note: Percentages are based on the number of non-missing observations within a treatment group for each variable.

Reviewer's comments:

Demographic characteristics (age, sex, race, iris color in the study eye) were well balanced across treatment groups within each study, as well as across studies.

6.1.3 Subject Disposition

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	**LE gel 0.38% BID (N=171)**	**LE gel 0.38% TID (N=171)**	**Vehicle BID & TID (N=199)**	**LE gel 0.38% BID (N=201)**	**LE gel 0.38% TID (N=200)**
Subjects Treated	172 (100.0%)	171 (100.0%)	170 (99.4%)	198 (99.5%)	201 (100%)	200 (100%)
As Randomized	172 (100.0%)	171 (100.0%)	170 (99.4%)	198 (99.5%)	201 (100%)	199 (99.5%)
Not as Randomized	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Included in ITT Popn [1]	172 (100.0%)	171 (100.0%)	171 (100.0%)	199 (100%)	201 (100%)	200 (100%)
Completed	80 (46.5%)	133 (77.8%)	139 (81.3%)	122 (61.3%)	145 (72.1%)	159 (79.5%)
Discontinued	92 (53.5%)	38 (22.2%)	32 (18.7%)	77 (38.7%)	56 (27.9%)	41 (20.5%)
Included in Safety Popn [2]	172 (100.0%)	171 (100.0%)	170 (99.4%)	198 (100%)	202 (100%)	199 (100%)
Completed	80 (46.5%)	133 (77.8%)	139 (81.3%)	122 (61.6%)	146 (72.3%)	158 (79.4%)
Discontinued	92 (53.5%)	38 (22.2%)	31 (18.1%)	76 (38.4%)	56 (27.7%)	41 (20.6%)
Included in PP Popn [3]	113 (65.7%)	133 (77.8%)	141 (82.5%)	139 (69.8%)	181 (90.0%)	168 (84.0%)
Completed Visit 5						
Yes	131 (76.2%)	161 (94.2%)	158 (92.4%)	160 (80.4%)	192 (95.5%)	189 (94.5%)
No	41 (23.8%)	10 (5.8%)	13 (7.6%)	39 (19.6%)	9 (4.5%)	11 (5.5%)
Completed Study through Visit 7						
Yes	80 (46.5%)	133 (77.8%)	139 (81.3%)	122 (61.3%)	145 (72.1%)	159 (79.5%)
No	92 (53.5%)	38 (22.2%)	32 (18.7%)	77 (38.7%)	56 (27.9%)	41 (20.5%)
Primary Reason for Premature Withdrawal for Subjects in ITT Popn						
Significant Protocol Dev. or Non-Compliance	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adverse Event	2 (1.2%)	1 (0.6%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (1.0%)
Rescue Therapy Use	88 (51.2%)	36 (21.1%)	31 (18.1%)	71 (35.7%)	49 (24.4%)	33 (16.5%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sponsor or Inv. Terminates the Study	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject Requests to be DC'ed from Study or is Lost to Follow Up	1 (0.6%)	1 (0.6%)	0 (0.0%)	1 (0.5%)	5 (2.5%)	5 (2.5%)
Inv. Discontinues Subject Participation	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	1 (0.6%)	3 (1.5%)	1 (0.5%)	1 (0.5%)

Abbreviations: LE, loteprednol etabonate (ophthalmic gel); BID, two times a day; TID, three times a day; ITT, intent-to-treat; PP, per protocol; N, number of subjects per treatment group; Dev, deviation; Inv., Investigator; Popn, Population; DC'ed, Discontinued
Note: Percentages are based on the number of subjects randomized within a treatment group, except for Safety Population, where percentages are based on number of subjects in their actual treatment group.
[1] All randomized subjects. Treatment assignments are based on treatment randomized.
[2] All subjects who received at least 1 dose of study drug. Treatment assignments are based on the treatment actually received.
[3] ITT subjects who remain in study through Visit 5 (Day 8) and who have not deviated from the protocol in any way likely to seriously affect the primary outcome of the study.

Reviewer's comments:

In both studies 842 and 875, a greater percentage of subjects in the LE gel TID group compared with the vehicle group completed Visit 5 (Postoperative Day 8). The difference in completers was due to a greater proportion of subjects in the vehicle group having been withdrawn from study participation for rescue therapy use.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoints for the Phase 3 studies were the proportion of subjects with complete resolution of anterior chamber cells (cell score = 0) in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle, and the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) for LE gel 0.38% and vehicle.

The primary analyses of the primary endpoints used the ITT population with missing values and post-rescue values imputed as treatment failures.

Proportion of Subjects with Complete Resolution of Anterior Chamber Cells and Complete Resolution of Ocular Pain in the Study Eye at Visit 5 (Postoperative Day 8); ITT Population

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	**LE gel 0.38% BID (N=171)**	**LE gel 0.38% TID (N=171)**	**Vehicle BID & TID (N=199)**	**LE gel 0.38% BID (N=201)**	**LE gel 0.38% TID (N=200)**
Complete Resolution of AC Cells in the Study Eye (Cell Score = 0)						
Yes, n(%)	16 (9.3%)	46 (26.9%)	49 (28.7%)	40 (20.1%)	52 (25.9%)	61 (30.5%)
No, n(%)	156 (90.7%)	125 (73.1%)	122 (71.3%)	159 (79.9%)	149 (74.1%)	139 (69.5%)
Difference [1] (95% CI)		17.6% (9.7%, 25.5%)	19.4% (11.3%, 27.4%)		5.8% (-2.5%, 14.0%)	10.4% (1.9%, 18.9%)
P-value [2]		<.0001	<.0001		0.1703	0.0169
Bonferroni-adjusted P-value		N/A	N/A		0.3407	0.0338
Adjusted P-value [3]		0.0001	<.0001		0.0927	0.0011
Complete Resolution of Ocular Pain in the Study Eye (Pain Score = 0)						
Yes, n(%)	82 (47.7%)	126 (73.7%)	125 (73.1%)	99 (49.7%)	151 (75.1%)	151 (75.5%)
No, n(%)	90 (52.3%)	45 (26.3%)	46 (26.9%)	100 (50.3%)	50 (24.9%)	49 (24.5%)
Difference [1] (95% CI)		26.0% (16.0%, 36.0%)	25.4% (15.4%, 35.4%)		25.4% (16.2%, 34.5%)	25.8% (16.6%, 34.9%)
P-value [2]		<.0001	<.0001		<.0001	<.0001
Bonferroni-adjusted P-value		N/A	N/A		0.3407	0.0338
Adjusted P- value [3]		<.0001	<.0001		<.0001	<.0001

Abbreviations: LE, loteprednol etabonate ophthalmic gel; BID, two times a day; TID, three times a day; ITT, intent-to-treat; N, number of subjects per treatment group; n, number of subjects in a resolution category; CI, confidence interval based on normal approximation; N/A, not applicable
[1] Difference in percent of subjects with complete resolution (LE gel 0.38% - Vehicle). [2] P-value comparing each LE 0.38% arm to Vehicle is from a Pearson Chi-squared test.
[3] Adjusted P-value comparing each LE gel 0.38% arm to vehicle is from a Cochran-Mantel-Haenszel test adjusting for site.

Reviewer's comments:

Results of two trials (Study 842 and Study 875) demonstrated that LE gel, 0.38% dosed TID was effective for the treatment of inflammation and ocular pain following cataract surgery.

In both trials, a significantly greater proportion of subjects in the LE gel TID treatment group compared with the vehicle group had complete resolution of anterior chamber cells at Visit 5 (Postoperative Day 8), and a significantly greater proportion of subjects in the LE gel TID treatment group compared with the vehicle group also had complete resolution of ocular pain at Visit 5 (Postoperative Day 8). For each of these primary endpoints, there was a statistically significant difference between the LE gel TID treatment group and vehicle within the prospectively-defined analysis population (i.e., intent-to-treat [ITT] population with missing data imputed as treatment failures).

6.1.5 Analysis of Secondary Endpoints(s)

Refer to Section 5.3.

Proportion of Subjects with Complete Resolution of Anterior Chamber Cells in the Study Eye by Visit; ITT Population

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	**LE gel 0.38% BID (N=171)**	**LE gel 0.38% TID (N=171)**	**Vehicle BID & TID (N=199)**	**LE gel 0.38% BID (N=201)**	**LE gel 0.38% TID (N=200)**
Visit 4 (Day 3), n(%)	N=172	N=171	N=171	N=199	N=201	N=200
Complete Resolution	12 (7.0%)	13 (7.6%)	7 (4.1%)	9 (4.5%)	17 (8.5%)	9 (4.5%)
Difference[1](95%CI)		0.6% (-4.9%,6.1%)	-2.9% (-7.7%,1.9%)		3.9% (0.9%,8.7%)	-0.0 (-4.1%,4.1%)
P-value[2]		0.8236	0.2431		0.1104	0.9913
Visit 5 (Day 8), n(%)	N=172	N=171	N=171	N=199	N=201	N=200
Complete Resolution	16 (9.3%)	46 (26.9%)	49 (28.7%)	40 (20.1%)	52 (25.9%)	61 (30.5%)
Difference[1](95%CI)		17.6% (9.7%,25.5%)	19.4% (11.3%,27.4%)		5.8% (-2.5%,14.0%)	10.4% (-1.9%,18.9%)
P-value[2]		<.0001	<.0001		0.1703	0.0169
Visit 6 (Day 15) n(%)	N=172	N=171	N=171	N=199	N=201	N=200
Complete Resolution	28 (16.3%)	73 (42.7%)	83 (48.5%)	64 (32.2%)	80 (39.8%)	93 (46.5%)
Difference[1](95%CI)		26.4% (17.2%,35.7%)	32.3% (23.0%,41.6%)		7.6% (-1.7%,17.0%)	14.3% (4.9%,23.8%)
P-value[2]		<.0001	<.0001		0.1115	0.0034
Visit 7 (Day 18) n(%)	N=172	N=171	N=171	N=199	N=201	N=200
Complete Resolution	40 (23.3%)	77 (45.0%)	91 (53.2%)	73 (36.7%)	76 (37.8%)	95 (47.5%)
Difference[1](95%CI)		21.8% (12.0%,31.5%)	30.0% (20.2%,39.7%)		1.1% (-8.3%,10.6%)	10.8% (1.2%,20.4%)
P-value[2]		<.0001	<.0001		0.8156	0.0287
Final On-Treatmnet Visit[3], n(%)	N=172	N=171	N=170	N=190	N=201	N=198
Complete Resolution	29 (16.9%)	74 (43.3%)	84 (49.4%)	67 (35.3%)	82 (40.8%)	94 (47.5%)
Difference[1](95%CI)		26.4% (17.1%,35.7%)	32.6% (23.2%,41.9%)		5.5% (-4.1%,15.1%)	12.2% (2.5%,21.9%)
P-value[2]		<.0001	<.0001		0.2602	0.0147

Abbreviations: LE, loteprednol etabonate ophthalmic gel; BID, two times a day; TID, three times a day; ITT, i ntent-to-treat; N, number of subjects per treatment group; n, number of subjects in a resolution category; CI, confidence interval based on normal approximation

Note: Complete resolution is defined as a score of 0.

[1] Difference in percent of subjects with complete resolution (LE 0.38% - Vehicle).

[2] P-value comparing each LE 0.38% arm to Vehicle is from a Pearson Chi-squared test.

[3] Last on-treatment visit for each subject, including any unscheduled visits, including Visit 6 (Day 15 +/- 1) as a regularly scheduled visit, and excluding any post-rescue visits.

Proportion of Subjects with Complete Resolution of Ocular Pain in the Study Eye by Visit; ITT Population

	Study 842			Study 875		
	Vehicle BID & TID (N=172)	**LE gel 0.38% BID (N=171)**	**LE gel 0.38% TID (N=171)**	**Vehicle BID & TID (N=199)**	**LE gel 0.38% BID (N=201)**	**LE gel 0.38% TID (N=200)**
Visit 4 (Day 3), n(%) Complete Resolution	N=172 96 (55.8%)	N=171 123 (71.9%)	N=171 117 (68.4%)	N=199 91 (45.7%)	N=201 143 (71.1%)	N=200 149 (74.5%)
Difference[1](95%CI)		16.1% (6.1%,26.1%)	-12.6% (2.4%,22.8%)		25.4% (16.1%,34.8%)	28.8% (19.6%,39.0%)
P-value[2]		0.0019	0.0161		<.0001	<.0001
Visit 5 (Day 8), n(%) Complete Resolution	N=172 82 (47.7%)	N=171 126 (73.7%)	N=171 125 (73.1%)	N=199 99 (49.7%)	N=201 151 (75.1%)	N=200 151 (75.5%)
Difference[1](95%CI)		26.0% (16.0%,36.0%)	25.4% (15.4%,35.4%)		25.4% (16.2%,34.5%)	25.8% (16.6%,34.9%)
P-value[2]		<.0001	<.0001		<.0001	<.0001
Visit 6 (Day 15) n(%) Complete Resolution	N=172 81 (47.1%)	N=171 129 (75.4%)	N=171 137 (80.1%)	N=199 105 (52.8%)	N=201 154 (76.6%)	N=200 158 (79.0%)
Difference[1](95%CI)		28.3% (18.5%,38.2%)	33.0% (23.5%,42.6%)		23.9% (14.8%,32.9%)	26.2% (17.3%,35.2%)
P-value[2]		<.0001	<.0001		<.0001	<.0001
Visit 7 (Day 18) n(%) Complete Resolution	N=172 73 (42.4%)	N=171 122 (71.3%)	N=171 122 (71.3%)	N=199 107 (53.8%)	N=201 140 (69.7%)	N=200 145 (72.5%)
Difference[1](95%CI)		28.9% (18.9%,38.9%)	28.9% (18.9%,39.9%)		15.9% (6.5%,25.3%)	18.7% (9.4%,28.0%)
P-value[2]		<.0001	<.0001		0.0011	0.0001
Final On-Treatmnet Visit[3], n(%) Complete Resolution	N=172 108 (62.8%)	N=171 138 (80.7%)	N=170 145 (85.3%)	N=190 122 (64.2%)	N=201 168 (83.6%)	N=198 170 (85.9%)
Difference[1](95%CI)		17.9% (8.6%,27.2%)	22.5% (13.5%,31.5%)		19.4% (10.8%,27.9%)	21.6% (13.3%,30.0%)
P-value[2]		<.0002	<.0001		<.0001	<.0001

Abbreviations: LE, loteprednol etabonate ophthalmic gel; BID, two times a day; TID, three times a day; ITT, intent-to-treat; N, number of subjects per treatment group; n, number of subjects in a resolution category; CI, confidence interval based on normal approximation **Note:** Complete resolution is defined as a score of 0.

[1] Difference in percent of subjects with complete resolution (LE 0.38% - Vehicle).
[2] P-value comparing each LE 0.38% arm to Vehicle is from a Pearson Chi-squared test.
[3] Last on-treatment visit for each subject, including any unscheduled visits, including Visit 6 (Day 15 +/- 1) as a regularly scheduled visit, and excluding any post-rescue visits.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Efficacy was explored among age groups < 65 years, ≥ 65 years to < 75 years, and ≥ 75 years. The proportion of subjects with complete resolution of anterior chamber cells was numerically greater in the LE gel TID group compared with the vehicle group

regardless of age group, and was nominally statistically significant in the age group of subjects ≥ 65 years to < 75 years, and ≥ 75 years age.

The proportion of subjects with complete resolution of ocular pain was nominally statistically significantly greater in the LE gel, 0.38% TID group compared with the vehicle group in all three age groups.

Efficacy was explored among sex groups (male, female). Regardless of gender, the proportion of subjects with complete resolution of anterior chamber cells and the proportion of subjects with complete resolution of ocular pain were nominally statistically significantly greater in the LE gel, 0.38% TID group compared with the vehicle group.

Efficacy was also explored among racial groups (white, non-white). The proportion of subjects with complete resolution of anterior chamber cells was numerically greater in the LE gel, 0.38% TID group compared with the vehicle group regardless of race, and was nominally statistically significant in the subgroup of white subjects. The proportion of subjects with complete resolution of ocular pain was significantly greater in the LE gel TID group compared with the vehicle group in both race subgroups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

TID dosing was noted to be more effective in BID in both Study 842 and 875.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

LE gel, 0.38% is intended for 14 days of dosing following ocular surgery.

In the Phase 3 studies with LE gel, 0.38%, even though anterior chamber inflammation and ocular pain following cataract surgery tends to be self-limiting, a lack of rebound inflammation can be inferred from the results of the Visit 7 (Postoperative Day 18) conducted 4 days after the last dose of study medication which was to be instilled the evening prior to Visit 6 (Postoperative Day 15).

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

2.6 7.1 Methods

The three phase 3 studies conducted with LE gel 0.38%, (Study 842, Study 843, and Study 875) were pooled for the integrated safety analyses pertaining to adverse events, visual acuity, biomicroscopy findings, fundoscopy, IOP, ocular symptoms, and drop

sensation. Study 842 and Study 875 included BID and TID dosing groups, and Study 843 only included a BID dosing group. Otherwise, the three studies used nearly identical protocols; therefore, the three studies were pooled for evaluating the safety of LE gel, 0.38% with respect to the extent of exposure, analysis of adverse events, and observations related to ocular safety and tolerance.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 7.1.

7.1.2 Categorization of Adverse Events

MedDRA 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.

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

The three phase 3 studies conducted with LE gel 0.38%, (Study 842, Study 843, and Study 875) were pooled for the integrated safety analyses.

7.2 Adequacy of Safety Assessments

The overall extent of exposure is based on the results of the pooled phase 3 studies. A total of 904 subjects were exposed to LE gel, 0.38% (535 of whom received BID treatment, and 369 of whom received TID treatment), and a total of 533 subjects received vehicle (BID or TID).

7.2.2 Explorations for Dose Response

Refer to Section 7.1. where BID dosing was not demonstrated to be effective and Section 6.1.4 which demonstrated TID dosing to be effective in Studies 842 and 875.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with LE Gel.

2.7 7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during any trial of Lotemax SM.

7.3.2 Nonfatal Serious Adverse Events

Non-Fatal SAE'S

Four subjects experienced a total of four serious adverse events. Two events were ocular and occurred in the subjects in the vehicle group, and two events were non-ocular, and occurred in the LE gel 0.38% BID group and vehicle group. No serious adverse events occurred in subjects in the LE gel 0.38% TID group.

Subject	Study	Preferred Term	Treatment Group	Eye	Study Day	
					Onset	Stop
(b) (6)	842	endophthalmitis	Vehicle	OD	day 7	ongoing
	842	small intestinal obstruction	LE gel BID	non-ocular	day 11	day 16
	843	endophthalmitis	Vehicle	OD	day 8	day 19
	875	hypokalaemia	Vehicle	non-ocular	day 16	day 18

7.3.3 Dropouts / Discontinuations

Study	Subject	Treatment Group	Adverse Event SOC//PT//Verbatim	Location
842	(b) (6)	LE 0.38% BID	Eye Disorders//Eye Inflammation// Inlfammation Left Eye	OS*
842		Vehicle BID	Eye Disorders//Eye Inflammation// Inflammation Eye	OD*
842		LE 0.38% BID	Eye Disorders//Eye Inflammation// Inflammation Right Eye	OD*
842		LE 0.38% TID	Eye Disorders//Eye Pain//Ocular Pain	OS*
842		Vehicle BID	Eye Disorders//Photophobia// Photophobia	OS*
842		Vehicle TID	Procedural Complications//Cataract Operation Complication//Retained Cortex	OD*
842		Vehicle TID	Infections And Infestations// Endophthalmitis//Endophthalmitis	OD*
842		Vehicle TID	Eye Disorders//Corneal Oedema// Corneal Edema	OD*
842		Vehicle BID	Eye Disorders//Macular Oedema// Macular Edema Os	OS*
842		Vehicle TID	General Disorders And Administration	OS*
842		LE 0.38% TID	Eye Disorders//Photophobia// Worsening Of Photophobia In Study Eye	OD*
842		LE 0.38% BID	Eye Disorders//Photophobia// Photophobia	OS*
843		Vehicle BID	Eye Disorders//Uveitis//Uveitis	OS*

843	(b) (6)	Vehicle BID	Eye Disorders//Corneal Oedema// Corneal Edema	OD*
843		Vehicle BID	Eye Disorders//Eye Pain//Eye Pain	OS*
843		LE 0.38% BID	Eye Disorders//Eye Pain//Eye Pain	OD*
843		Vehicle BID	Eye Disorders//Eye Pain//Increasing Ocular Pain	OD*
		Vehicle BID	Eye Disorders//Corneal Oedema// Corneal Edema	OD*
			Eye Disorders//Eye Inflammation// Overall Inflammation Of Study Eye	OD*
843		Vehicle BID	Eye Disorders//Eye Inflammation// Ocular Inflamation	OS*
843		Vehicle BID	Eye Disorders//Photophobia// Worsening Photophobia	OS*
843		Vehicle BID	Eye Disorders//Ocular Discomfort// Increased Discomfort In Study Eye	OD*
			Eye Disorders//Photophobia//Increased Photophobia In Study Eye	OD*
843		LE 0.38% BID	Eye Disorders//Macular Oedema// Macular Edema	OD
			Eye Disorders//Macular Oedema// Macular Edema	OS*
843		Vehicle BID	Infections And Infestations// Endophthalmitis//Endophthalmitis	OD*
843		Vehicle BID	Eye Disorders//Corneal Oedema// Corneal Edema Od	OD*
843		Vehicle BID	Eye Disorders//Eye Pain//Pain In Os	OS*
843		Vehicle BID	Eye Disorders//Eye Oedema// Ocular Edema	OD*
843		Vehicle BID	Eye Disorders//Eye Pain//Patient's Complaint Of Pain In Study Eye	OS*
			Eye Disorders//Eyelid Oedema// Patient's Complaint Of Eyelid Swelling In Study Eye	OS*
843		Vehicle BID	Eye Disorders//Iritis//Iritis	OD*
843		Vehicle BID	Eye Disorders//Iritis//Iritis	OD*
875		LE 0.38% TID	Investigations//Intraocular Pressure Increased//Elevated Intraocular Pressure	OS*
875		Vehicle TID	Eye Disorders//Iritis//Plastic Iritis	OD*
875		LE 0.38% BID	Skin and Subcutaneous Tissue Disorders//Rash//Facial Rash	Non-ocular
875		LE 0.38% BID	Respiratory, Thoracic and Mediastinal Disorders//Allergic Sinusitis// Worsening of Sinus Allergies	Non-ocular
			Respiratory, Thoracic and Mediastinal Disorders//Asthma//Worsening of Asthma	Non-ocular
875		LE 0.38% TID	Investigations//Blood Pressure Increased//Elevated Blood Pressure	Non-ocular

			Nervous System Disorders// Headache// Headache	Non-ocular
875	(b) (6)	LE 0.38% TID	Infections and Infestations//Bronchitis// Acute Bronchitis	Non-ocular

Abbreviations: LE, loteprednol etabonate; BID, bis in die, twice a day; TID, ter in die, three times a day; OD, oculus dexter, right eye; OS, oculus sinister, left eye The study eye is indicated by an *
Source: Listing 16.2.7.4 in Study 842 CSR; Listing 16.2.7.4 in Study 843 CSR; Listing 16.2.7.4 in Study 875 CSR

Reviewer's Comments:

These adverse reactions are either consistent with the age or general findings in the population of subjects undergoing cataract extraction.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Ocular Adverse Events (≥1% in Any Treatment Group) in the Study Eye -- Safety Population

Table 2.7.4.5–2: Common Ocular Adverse Events (≥1% in Any Treatment Group) in the Study Eye -- Safety Population

Systerm Organ Class Preferred Term	Vehicle N=533 n (%) [Events]	LE 0.38% BID N=535 n (%) [Events]	LE 0.38% TID N=369 n (%) [Events]	All LE Gel N=904 n (%) [Events]
Pooled for Studies 842, 843 and 875				
Eye disorders				
Photophobia	12 (2.3) [14]	6 (1.1) [6]	3 (0.8) [3]	9 (1.0) [9]
Eye pain	14 (2.6) [15]	7 (1.3) [9]	1 (0.3) [1]	8 (0.9) [10]
Conjunctival hyperaemia	6 (1.1) [9]	2 (0.4) [2]	[0]	2 (0.2) [2]
Corneal oedema	9 (1.7) [9]	[0]	[0]	[0]

Abbreviations: LE, loteprednol etabonate ophthalmic gel, 0.38%; N, number of subjects per treatment group; n, number of subjects in a specific category; TEAE, treatment emergent adverse event
Notes: At each level of summation (overall, system organ class, preferred term), subjects reporting more than 1 adverse event are counted only once. Percentages are based on the number of subjects in the Safety Population. The number in brackets represents the total number of events reported. Adverse events are coded using MedDRA Version 16.1.
Source: ISS Table 14.3.2.1

Non-Ocular Adverse Events

All non-ocular treatment-emergent adverse events were reported in less than 1.0% of subjects in each treatment group (refer to ISS Table 14.3.1.1). The most common non-ocular event was headache (vehicle: 0.9%, 5/533; LE gel BID: 0.2%, 1/535; LE gel TID: 0.8%, 3/369). All other non-ocular events, with the exception of bronchitis, upper respiratory tract infection, and nasopharyngitis, were reported in single subjects in only one of the 3 treatment groups.

(b) (4)
Version: Final

Valeant Pharmaceuticals North America, LLC.
Study: Integrated Summary of Safety

14.3.1.1
Treatment Emergent Non-Ocular Adverse Event
Safety Population

System Organ Class Preferred Term	Vehicle N=533 n (%) [Evt]	LE 0.38% BID N=535 n (%) [Evt]	LE 0.38% TID N=369 n (%) [Evt]	All LE Gel N=904 n (%) [Evt]
Pooled for Studies 842, 843 and 875				
Subjects Reporting at Least One TEAE	12 (2.3) [14]	15 (2.8) [19]	9 (2.4) [12]	24 (2.7) [31]
Infections and infestations	3 (0.6) [3]	6 (1.1) [6]	3 (0.8) [3]	9 (1.0) [9]
Bronchitis	1 (0.2) [1]	1 (0.2) [1]	2 (0.5) [2]	3 (0.3) [3]
Nasopharyngitis	[0]	1 (0.2) [1]	1 (0.3) [1]	2 (0.2) [2]
Cellulitis	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Rash pustular	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Upper respiratory tract infection	1 (0.2) [1]	1 (0.2) [1]	[0]	1 (0.1) [1]
Urinary tract infection	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Sinusitis	1 (0.2) [1]	[0]	[0]	[0]
Nervous system disorders	6 (1.1) [6]	2 (0.4) [2]	3 (0.8) [3]	5 (0.6) [5]
Headache	5 (0.9) [5]	1 (0.2) [1]	3 (0.8) [3]	4 (0.4) [4]
Dizziness	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Migraine with aura	1 (0.2) [1]	[0]	[0]	[0]
General disorders and administration site conditions	[0]	1 (0.2) [1]	3 (0.8) [3]	4 (0.4) [4]
Fatigue	[0]	[0]	1 (0.3) [1]	1 (0.1) [1]
Malaise	[0]	[0]	1 (0.3) [1]	1 (0.1) [1]
Product taste abnormal	[0]	[0]	1 (0.3) [1]	1 (0.1) [1]
Pyrexia	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Respiratory, thoracic and mediastinal disorders	1 (0.2) [1]	3 (0.6) [4]	1 (0.3) [1]	4 (0.4) [5]
Allergic sinusitis	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Asthma	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]
Cough	[0]	1 (0.2) [1]	[0]	1 (0.1) [1]

Abbreviations: Evt, Event; LE, loteprednol etabonate ophthalmic gel, 0.38%; N, number of subjects per treatment group; n, number of subjects in a specific category; TEAE, treatment emergent adverse event
Notes:
1. At each level of summation (overall, system organ class, preferred term), subjects reporting more than 1 adverse event are counted only once. Percentages are based on the number of subjects in the Safety Population.
2. The number in brackets represents the total number of events reported.
3. Adverse events are coded using MedDRA Version 16.1.
Reference: Listing 16.2.7

(b) (4)

Page 1 of 3

Reviewer's Comments:

These adverse reactions are either consistent with the age or general findings in the population of subjects undergoing cataract extraction.

7.4.2 Laboratory Findings

Clinical laboratory evaluations (hematology, serum chemistry, urinalysis) were performed on healthy volunteers in the PK studies (Study 864 and Study 881) with LE gel, 0.38%. There were no abnormal results.

7.4.3 Vital Signs

Systolic and diastolic blood pressure, and heart rate, respiratory rate were evaluated at Visit 1 (Screening/Baseline), and at Visit 2 (Day 1) and Visit 3 (Day 14 to 16) at 5 minutes and 2.7.4 Summary of Clinical Safety 8 hours (Study 881) or 10 hours (Study 864) post-study drug administration in the clinical PK studies conducted with LE gel,

0.38%. Additionally, temperature was assessed at Visit 1 (Screening) in these studies to qualify subjects for study participation.

No abnormal findings were noted for systolic and diastolic blood pressure, heart rate, or respiratory rate for any subject.

7.4.4 Electrocardiograms (ECGs)

Refer to Section 7.4.3.

7.4.5 Special Safety Studies/Clinical Trials

Corticosteroids have a known risk of increasing IOP and therefore IOP was monitored at every visit.

Reviewer's Comments:

The IOP findings are consistent with the age and general findings in the population of subjects undergoing cataract extraction.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A dose dependency was not found. Refer to Section 7.4.1.

7.5.2 Time Dependency for Adverse Events

Corticosteroids are known to increase risk of IOP elevation based on duration of exposure.

7.5.3 Drug-Demographic Interactions

The assessment of the AEs reported during trials of Lotemax SM showed no evidence of any clinically relevant differences by gender or age group.

7.5.4 Drug-Disease Interactions

Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses.

Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

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.

2.8 7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable as product is for short term use only.

7.6.2 Human Reproduction and Pregnancy Data

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

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric studies have been conducted with LOTEMAX SM. In a trial to evaluate the safety and efficacy of Lotemax gel, 0.5% in pediatric subjects 0 – 11 years of age, Lotemax gel, 0.5% demonstrated non-inferiority to Prednisolone Acetate Ophthalmic suspension, 1% for the treatment of intraocular inflammation following childhood cataract surgery.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Lotemax SM is a non-narcotic and does not have abuse potential.

7.7 Additional Submissions / Safety Issues

The 120 Day Safety was reported. There was no additional data to report as the studies had been completed at time of submission.

8 Postmarketing Experience

LE gel, 0.38% is not marketed currently in any country.

9.0 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

Refer to recommended edits in attached label.

9.3 Advisory Committee Meeting

No new issues that were thought to benefit from an Advisory Committee discussion.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 208219
Submission Date(s): April 25, 2018
Applicant: Bausch Health, Inc.
Product: Loteprednol etabonate ophthalmic gel, 0.38%
Reviewer: Martin P Nevitt, M.D., M.P.H.
Date of Review: December 10, 2018
Covered Clinical Study (Name and/or Number): Studies 842, 843 and 875.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 136		
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): 8		
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: 8 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) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

To minimize potential bias, the studies were randomized with the investigators and subjects masked to treatment and mulit-center where no investigator enrolled a majority of subjects.

Note: Overall only (b) (6) eyes were enrolled at the sites that had some form of compensation:

Investigator / Sub-investigator	Site	Eyes Enrolled in Study 842	Eyes Enrolled in Study 875
(b) (6)			Not in study
			Not in study
			Not in study

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

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