A Phase 3, 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

PROTOCOL

STUDY #875

IND #102654

Sponsor:

Bausch & Lomb Incorporated

This clinical investigation is being conducted in accordance with 21CFR Parts 11, 50, 54, 56 and 312, 42 USC 282(j), ICH GCPs, and applicable local regulations.

Revision Chronology:

Original	10 Sep 2015
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SPONSOR APPROVAL PAGE

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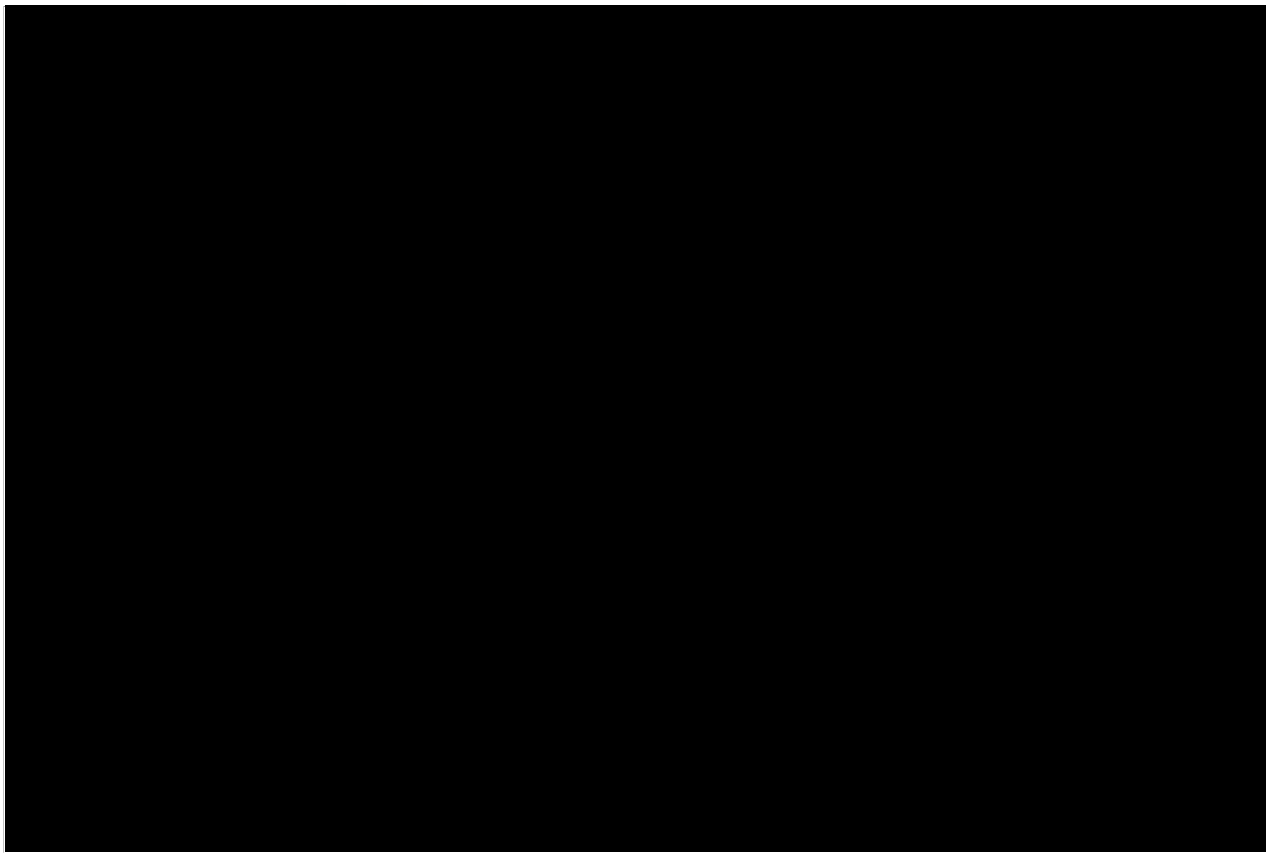
Approved By:



INVESTIGATOR STATEMENT OF APPROVAL

A Phase 3, 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

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I have read the attached document, concur that it contains all information necessary to conduct the study, and agree to abide by all provisions set forth therein.

I agree to conduct this study in accordance with 21CFR Parts 11, 50, 54, 56 a nd 312, 42 U SC 282(j), ICH GCPs, and applicable local regulations. I will not initiate the study until I have obtained written approval by the appropriate IRB/EC and have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor. I will obtain written informed consent (and, if applicable, assent for children) from each study subject prior to performing any study specific procedures.

I understand that my signature on a case report form indicates that the data therein has been reviewed and accepted by me.

I understand that this document and related information is subject to confidentiality terms found in my signed Confidentiality or Clinical Services Agreement. I agree to protect the confidentiality of my patients when allowing the Sponsor of this clinical investigation, and/or relevant regulatory authorities and IRB/ECs, direct access to my medical records for study subjects.

_____

Principal Investigator, Printed Name

_____ _____

Principal Investigator, Signature Date

Upon signing, provide the original signed page to Bausch & Lomb Incorporated and retain a copy for your files.

PERSONNEL AND FACILITIES

NOTE: The information on this page is subject to change. All changes will be provided under separate cover.

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APPENDICES

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Term
AC	Anterior Chamber
AE	Adverse Event
BAK	Benzalkonium Chloride
Bausch + Lomb	Bausch & Lomb Incorporated
BID	Twice per day
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
EC	Ethics Committee
FDA	United States Food and Drug Administration
GCPs	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LDPE	Low Density Polyethylene
LE	Loteprednol etabonate
LE gel 0.38%	Loteprednol etabonate ophthalmic gel, 0.38%
LOCF	Last observation carried forward
mmHg	Millimeters of mercury
NSAID	Nonsteroidal Anti-Inflammatory Drug
OTC	Over the counter
PK	Pharmacokinetic
PP	Per protocol
ppm	Parts per million
PRN	As needed
SAE	Serious Adverse Event
SD	Standard deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event

TID	Three times per day
USC	United States Code
VA	Visual Acuity

NOTE: The first occurrence of some abbreviations is not spelled out in the document (eg, units of measure).

SYNOPSIS

Bausch & Lomb Incorporated Study #875	
Title:	**A Phase 3, 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**
Phase of study:	3
Number of subjects:	Total enrollment for this study is approximately 588 subjects at approximately 60 investigative sites in the United States (US).
Planned study period and duration of treatment:	Eligible subjects who are enrolled in the study will be seen for 7 scheduled study visits over the course of approximately 4 weeks. Treatment duration for this study will be approximately 14 days.
Objective(s):	The primary objective is to evaluate the safety and efficacy of loteprednol etabonate ophthalmic gel, 0.38% (BID and TID) for the treatment of postoperative inflammation and pain following cataract surgery.
Study design:	This is a multi-center, randomized, double-masked, vehicle-controlled study. The study duration will be approximately 4 weeks from the screening assessment (Visit 1) to the last visit (Visit 7 [Postoperative Day 18]). Subjects will visit the clinic approximately 7 times. Visit 1 shall occur no earlier than 14 days prior to surgery. The Visit 1 date will be the date on which the first screening assessment is performed The informed consent date may be the same as or prior to visit 1(screening as sessent date). Visit 2 will be on the day of surgery. At Visit 3 (Postoperative Day 1), eligibility for randomization into the study will be assessed. If eligible, subjects will be randomized and will complete postoperative study Visits 4, 5, 6, and 7 (Postoperative Days 3, 8, 15, and 18, respectively). Efficacy will be assessed at Visits 4, 5, and 6 (Postoperative Days 3, 8, and 15, respectively). Additionally, a post-treatment exam will be provided at Visit 7 (Postoperative Day 18). Approximately 588 subjects will be randomized in a 2:2:1:1 ratio to loteprednol etabonate (LE) gel 0.38% TID, LE gel 0.38% BID, vehicle TID, and vehicle BID. The 2 vehicle arms will be combined into 1 treatment group in the statistical analysis, and hence the study will have 3 treatment groups, ie, LE gel 0.38% TID, LE gel 0.38% BID, and (combined) vehicle groups. Each treatment group will consists of approximately 196 subjects. Subjects randomized to BID groups will instill 1 drop of study drug into the study eye, 2 times per day, at approximately 12 h our intervals. Subjects randomized to TID groups will instill 1 drop of study drug into the study eye, 3 times per day, at approximately 8 hour intervals. The initial dose will occur in the clinic at Visit 3 (Postoperative Day 1). Study treatment will last approximately 14 days with the last dose administered on the evening before Visit 6 (Postoperative Day 15).
Study endpoints:	**Primary Efficacy Endpoints** The primary efficacy endpoints for this study are: 1. The proportion of subjects with complete resolution of anterior chamber (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

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	(Postoperative Day 8) for LE gel 0.38% and vehicle **Secondary Efficacy Endpoints** • 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 AC cells and 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 • Proportion of treatment failures at Visit 5 (Postoperative Day 8) **Safety Endpoints:** • Incidence of ocular and non-ocular adverse events (AEs) • Change in intraocular pressure (IOP) • Ocular signs (biomicroscopy) • Change in visual acuity (VA) • Change in dilated fundus exam **Tolerability Endpoints:** • Study drug sensation assessment at Visit 5 (Postoperative Day 8) • Ocular symptoms at each follow-up visit
Criteria for inclusion:	To be enrolled in this study, each subject must: **Visit 1 (Screening) Criteria** 1. Be 18 years or older on the date the Informed Consent Form (ICF) is signed and with the capacity to provide voluntary informed consent. 2. Be able to read, understand, and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF and provide Health Insurance Portability and Accountability Act (HIPAA) authorization. 3. Be willing and able to comply with all treatment and follow-up/study procedures. 4. Be a can didate 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, have 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 be postmenopausal at least 12 months prior to Visit 3 or permanently sterilized [eg, tubal occlusion, hysterectomy, bilateral salpingectomy])

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	or – Have 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, agree to use adequate contraceptive methods prior to and during the study treatment period, as described below. – Female subjects of childbearing potential must use at least 1 form of the following acceptable contraceptive methods: o 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 medication) o True abstinence (when this is in line with the preferred and usual lifestyle of the subject) o Placement of a copper-containing IUD prior to Visit 3 o Condom with spermicidal foam/gel/film/cream/suppository at least 14 days prior to Visit 3 o Male partner who had a vasectomy at least 3 months prior to Visit 3 – Male subjects with partners of childbearing potential must use at least 1 form of the following acceptable contraceptive methods: o True abstinence (When this is in line with the preferred and usual lifestyle of the subject) o Vasectomy at least 3 months prior to Visit 3 o Without a vasectomy, must use a condom with spermicidal foam/gel/film/cream/suppository 8. Be willing to postpone cataract surgery on the fellow eye until after study completion. **Visit 3 (Postoperative Day 1) Criteria** 9. Have undergone 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** – Not be of childbearing potential (female subjects not of childbearing potential must be postmenopausal at least 12 months prior to Visit 3 or permanently sterilized [eg, tubal occlusion, hysterectomy, bilateral salpingectomy]) or – Have a negative urine pregnancy test result at Visit 3 (Postoperative Day 1). 11. Continue to meet all requirements of Inclusion Criterion #7. 12. Have ≥ Grade 2 AC cells (6-15 cells) in the study eye.
Criteria for exclusion:	To be enrolled in this study, each subject must not: 1. Have a severe/serious ocular condition or history/presence of chronic generalized systemic disease that the Investigator feels might increase the risk to the subject or confound the result(s) of the study.

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	2. Be a female subject who is pregnant or breastfeeding. 3. Have ocular hypertension (IOP ≥ 21 mmHg), glaucoma, or any glaucoma-related incisional or laser surgery in the study eye. *Note: this exclusion criterion must apply to both Visit 1 (Screening) and Visit 3 (Postoperative Day 1).* 4. Be monocular (fellow eye is nonfunctional or fellow eye's pinhole vision is worse than Snellen 20/200). 5. Have 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. Have a current diagnosis of cystoid macular edema in the study eye. 7. Have any abnormality that prevents reliable Goldmann applanation tonometry in either eye. 8. Have iris atrophy in the operative eye. 9. Have lens pseudoexfoliation syndrome with glaucoma or zonular compromise in the study eye. 10. Be unable, for any reason, to discontinue contact lens use in the study eye during the course of the study. 11. Have 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. Have proliferative diabetic retinopathy or moderate to severe non-proliferative diabetic retinopathy in the study eye. 13. Have 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. Have a congenital ocular anomaly in either eye. 15. Have a presence of active external ocular disease: infection (bacterial, viral or fungal) or inflammation (including allergic) of the study eye. 16. Have used ocular therapy (either eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, antihistamines, or decongestants within 2 days prior to surgery or be expected to require any of these treatments during the 18 days following cataract surgery. 17. Be 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. Be expected to require treatment with any systemic, inhalation, nasal, or ocular (either eye) corticosteroids or glucocorticoids during the 18 da ys following cataract surgery or have used any systemic or ocular corticosteroids within 14 days prior to cataract surgery. Dermal use outside the ocular area is permitted. 19. Be expected to require concurrent systemic or ocular therapy with immunosuppressants (eg, Restasis) during the 18 days following cataract surgery or have used ocular immunosuppressants within 30 da ys prior to surgery. 20. Have known hypersensitivity or contraindication to the study drug(s) or their components. 21. Have participated in any drug or device clinical investigation within 30 days

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	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. Have been previously randomized in this study. 23. Currently require or be expected to require treatment with any medication listed as a disallowed medication per the Disallowed Therapy Section of this protocol.
Investigational product, dose, and mode of administration:	The test article, loteprednol etabonate ophthalmic gel, 0.38%, contains the active ingredient loteprednol etabonate, 0.38%, and the preservative benzalkonium chloride, 0.003%. It also contains the inactive ingredients boric acid, edetate disodium dihydrate, glycerin, hypromellose, poloxamer 407, polycarbophil, propylene glycol, sodium chloride, sodium hydroxide, and water for injection. For BID dosing, subjects will administer 1 drop of LE gel in the study eye 2 times per day at approximately 12 hour intervals. For TID dosing, subjects will administer 1 drop of LE gel in the study eye 3 times per day at approximately 8 hour intervals.
Comparator product, dose, and mode of administration:	The comparator, vehicle of loteprednol etabonate ophthalmic gel, contains the preservative benzalkonium chloride 0.003% and the inactive ingredients boric acid, edetate disodium dihydrate, glycerin, hypromellose, poloxamer 407, polycarbophil, propylene glycol, sodium chloride, sodium hydroxide, and water for injection. For BID dosing, subjects will administer 1 drop of vehicle in the study eye 2 times per day at approximately 12 hour intervals. For TID dosing, subjects will administer 1 drop of vehicle in the study eye 3 times per day at approximately 8 hour intervals.
Rescue therapy	Subjects will be assessed at Visits 4 through 7 (Postoperative Days 3, 8, 15, and 18) for treatment rescue. Subjects with worsening or no change in the grade of inflammation in the study eye compared with the previous visit are eligible and may be considered for rescue medication at the discretion of the Investigator.
Study procedures:	**Visit 1: Screening Assessments** ***NOTE:*** *Visit 1 shall occur no earlier than 14 days prior to surgery. The Visit 1 date will be the date on which the first screening assessment is performed. The informed consent date may be the same as or prior to visit 1(screening assessent date).* • Obtain written informed consent and HIPAA authorization • Determine if the subject meets preliminary eligibility criteria – Collect demographic information – Collect current and relevant medical and ophthalmic history – Identify concomitant medications used – Perform a urine pregnancy test, as applicable • If the subject meets the preliminary eligibility criteria, the following screening assessments will be performed: – Perform a clinical assessment of ocular symptoms – Perform assessment of pin-holed Snellen VA – Perform biomicroscopy assessment – Perform IOP measurement (measurement of IOP must occur after the

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	assessment of ocular symptoms and biomicroscopy) – Perform dilated fundus exam • Collect and record AEs ***NOTE:*** *Surgery will be scheduled to occur ≤ 14 days from the Screening Assessment. Screening and surgery cannot take place on the same day.* **Visit 2: Surgery (≤ 14 days from the Screening Assessment)** The following must be performed prior to the surgery: • Collect and record AEs and changes in concomitant medications. ***NOTE:*** *Following surgery, subjects may only receive antibiotics and will be scheduled to return in 18 to 34 hours to determine if they have sufficient ocular inflammation to be included in the study (see Inclusion Criteria #12). Subjects who do not receive a posterior chamber IOL or who, in the Investigator's opinion, have complications such that it is not in the subject's best interests to continue in the study are considered screen failures.* ***NOTE:*** *If during the surgery it is determined that additional manipulations, such as pupil stretching or the use of iris hooks or peripheral relaxing corneal incisions are required, the subject is not eligible to participate in the trial.* **Visit 3: Postoperative Day 1 (Randomization [18 to 34 hours post-surgery])** ***NOTE:*** *Post-surgery visits should be scheduled so that IOP can be assessed within ±2 hours of the time of IOP assessment on Visit 1.* ***NOTE:*** *Unmasked study staff personnel will be designated for study drug handling, including dispensing to subjects, training subjects on dosing administration, and collection/review of study diaries at each visit (Section 4.6).* • Perform a urine pregnancy test, as applicable • Perform a clinical assessment of ocular symptoms • Perform assessment of pin-holed Snellen VA • Perform biomicroscopy assessment – Assess AC cells (refer to Appendix B) ▪ If the AC cell grade is ≥ 2, then the subject is eligible and will be randomized. ▪ If the AC cell grade is < 2, then the subject is not eligible and will be a screen failure. • Perform IOP measurement – IOP should be assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy. – If a one-time intervention is necessary to reduce IOP prior to randomization (eg, 'burping' the paracentesis, Diamox, or topical hypotensive agent) and the pressure returns to normal, the subject can be randomized into the study. The AE and intervention should be recorded on the appropriate logs (eg, Adverse Event, Concomitant Medication, and Ocular Surgical Intervention) and the final IOP

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	measured prior to randomization should be recorded in the eCRF. • Randomize eligible subjects by assigning the next applicable subject kit number • Dispense study drug kit to the subject • Instruct the subject to instill 1 drop of study drug into the study eye according to the instructions provided with the kit. – Subjects should instill their initial dose while in the clinic to ensure that they understand and are able to follow instructions for instillation. – The Investigator and study staff involved in assessments of safety and efficacy must not be present during the in-office study drug instillation. – Remind subjects to instill all doses on Day 1 even if the interval between doses is shorter than described in the kit instructions. – For those subjects receiving a topical antibiotic, remind the subject that the topical antibiotic drops must be instilled a minimum of 15 minutes BEFORE study drug application. • Collect and record AEs and changes in concomitant medications • Provide a Study Drug Administration Diary to the subject. Instruct the subject to record each instillation in the diary and to bring the diary and study drug (all bottles) to the next visit. Remind the subject that no other information should be recorded in the diary. **Visit 4: Postoperative Day 3 (±1 Day)** ***NOTE:*** *Post-surgery visits should be scheduled so that IOP can be assessed within ±2 hours of the time of IOP assessment on Visit 1.* • Perform a clinical assessment of ocular symptoms • Perform assessment of pin-holed Snellen VA • Perform biomicroscopy assessment • Perform IOP measurement – IOP should be assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy. • Collect and record AEs and changes in concomitant medications • Collect and review the Study Drug Administration Diary for accuracy and compliance. Dispense a new Study Drug Administration Diary. Instruct the subject to record the time of each instillation in the diary and to bring the diary and study drug (all bottles) to the next visit. Remind the subject that no other information should be recorded on the diary. • Remind the subject to instill 1 drop of study drug into the study eye according to the instructions provided with the kit. For those subjects receiving a topical antibiotic, remind the subject that the topical antibiotic drops must be instilled a minimum of 15 minutes BEFORE study drug application. ***NOTE:*** *Subjects will be assessed at Visits 4 through 7 (Postoperative Days 3, 8, 15, and 18) for treatment rescue. Subjects with worsening or no change in the grade of inflammation in the study eye compared with the*

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	previous visit are eligible and may be considered for rescue medication at the discretion of the Investigator. The choice of rescue medication and dosing shall be determined by the Investigator. See Section 6.2.3.1 for more details. **Visit 5: Postoperative Day 8 (±1 Day)** ***NOTE:*** *Post-surgery visits should be scheduled so that IOP can be assessed within ±2 hours of the time of IOP assessment on Visit 1.* • Perform a clinical assessment of ocular symptoms • Perform study drug sensation assessment • Perform assessment of pin-holed Snellen VA • Perform biomicroscopy assessment • Perform IOP measurement – IOP should be assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy. • Collect and record AEs and changes in concomitant medications • Collect and review the Study Drug Administration Diary for accuracy and compliance. Dispense a new Study Drug Administration Diary. Instruct the subject to record the time of each instillation in the diary and to bring the diary and study drug (both bottles) to the next visit. Remind the subject that no other information should be recorded on the diary. • Remind the subject to instill 1 drop of study drug into the study eye according to the instructions provided with the kit. For those subjects receiving a topical antibiotic, remind the subject that the topical antibiotic drops must be instilled a minimum of 15 minutes BEFORE study drug application • Remind the subject that the last instillation of study drug will occur the evening before Visit 6. **Visit 6: Postoperative Day 15 (±1 Day), (End of treatment)** ***NOTE:*** *Post-surgery visits should be scheduled so that IOP can be assessed within ±2 hours of the time of IOP assessment on Visit 1.* • Perform a clinical assessment of ocular symptoms • Perform assessment of pin-holed Snellen VA • Perform biomicroscopy assessment • Perform IOP measurement – IOP should be assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy. • Perform dilated fundus examination • Collect and record AEs and changes in concomitant medications • Collect and review the Study Drug Administration Diary for accuracy and compliance • Collect all used and unused study drug (all bottles) from the subject **Visit 7: Postoperative Day 18 (±1 Day), (Post-treatment exam)**

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	NOTE: *Post-surgery visits should be scheduled so that IOP can be assessed within ±2 hours of the time of IOP assessment on Visit 1.* • Perform a urine pregnancy test, as applicable • Perform a clinical assessment of ocular symptoms • Perform assessment of pin-holed Snellen VA • Perform biomicroscopy assessment • Perform IOP measurement – IOP should be assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy. • Collect and record AEs and changes in concomitant medications • Exit the subject from the study
Statistical Methods:	**Sample Size** Approximately 588 subjects will be randomized in a 2:2:1:1 ratio to LE gel 0.38% TID, LE gel 0.38% BID, vehicle TID, and vehicle BID. The 2 vehicle arms will be combined into 1 treatment group in the statistical analysis, and hence the study will have 3 treatment groups, ie, LE gel 0.38% TID, LE gel 0.38% BID, and (combined) vehicle groups. Each of the three treatment groups will consist of approximately 196 subjects. Regarding complete resolution of AC cells, a sample size of 196 subjects will provide 87% power to detect each of the two expected differences (BID and TID dosing). The two simultaneous tests will have 95% power to detect at least one of the two differences and 80% power to detect both differences. Under the planned gatekeeping hypothesis testing strategy, the power of each pain resolution hypothesis is limited by the power of the corresponding AC cells resolution hypothesis. In the event that the corresponding AC cells hypothesis is rejected, each pain hypothesis test has 99% power to detect the expected difference. Estimates of efficacy used to calculate the sample size were based on the integrated database of 4 previous similar studies. Two of these studies were conducted with LE gel 0.5% QID and vehicle. One study was conducted with LE gel, 0.38%, dosed TID and BID. One study was conducted with LE gel, 0.38%, dosed BID. **Primary Endpoints** The primary efficacy endpoints for this study are: 1. The proportion of subjects with complete resolution of anterior chamber (AC) cells at Visit 5 (Postoperative Day 8). 2. The proportion of subjects with Grade 0 pain at Visit 5 (Postoperative Day 8). **Secondary Endpoints** The secondary endpoints for this study are: • Proportion of study eyes with complete resolution of AC cells at each visit and for each subject's final on-treatment visit. • Proportion of study eyes with Grade 0 pain at each visit and for each subject's final on-treatment visit. • Proportion of study eyes with complete resolution of AC flare at each visit

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	and for each subject's final on-treatment visit. • Proportion of study eyes with complete resolution of AC cells and flare 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. **Safety Endpoints** The safety endpoints for this study are: • Incidence of ocular and non-ocular AEs • Change in IOP • Ocular signs (biomicroscopy) • Change in VA • Change in dilated fundus exam **Tolerability Endpoints** The tolerability endpoints for this study are: • Study drug sensation assessment at Visit 5 (Postoperative Day 8) • Ocular symptoms at each follow-up visit **General Statistical Considerations** Summaries for continuous variables will include the sample size, mean, SD, median, minimum, and maximum. Minimums and maximums will be reported with the same precision as the raw values; medians and means will have 1 more decimal place; SD will have 2 more decimal places. Summaries for discrete variables will include the tabulation of frequencies and percentages. Differences between treatment groups will be calculated as LE gel 0.38% minus vehicle, and change from baseline will be calculated as follow-up visit minus baseline. The baseline visit will be defined as Visit 3 (Postoperative Day 1). For IOP, change from the previous visit will also be summarized. **Hypotheses** The following multiple endpoints and multiple dose-vehicle comparison hypotheses will be tested using Bonferroni-based tree structured gatekeeping tests to control the overall type I error rate ($\alpha = 0.05$) for the primary efficacy endpoints over the entire study. [32, 33] The hypotheses in Family 1 will be tested simultaneously. Each hypothesis in Family 2 will be eligible for rejection only if the corresponding hypothesis (TID, BID) in Family 1 is rejected. ***Family 1 of Hypotheses: Complete Resolution of AC Cells in the Study Eye at Visit 5*** H_{011}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) = 0. H_{A11}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed TID. H_{012}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) = 0.

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	H_{A12}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed BID. ***Family 2 of Hypotheses: Complete Resolution of Pain in the Study Eye at Visit 5*** H_{021}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) = 0. H_{A21}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed TID. H_{022}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) = 0. H_{A22}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed BID. **Analysis of Primary Efficacy Endpoints** The primary efficacy endpoints are the proportion of subjects with complete resolution of AC cells at Visit 5 (Postoperative Day 8) and the proportion of subjects with Grade 0 pain at Visit 5 (Postoperative Day 8). Primary efficacy analyses will be based on the intent-to-treat (ITT) population with missing data imputed as failures (subjects placed on rescue medication prior to the visit being summarized will also be considered failures). The primary efficacy analyses of the difference between each active treatment group and the combined vehicle treatment group at (Visit 5) Postoperative Day 8 will be tested using Pearson Chi-squared tests with p-values adjusted using a Bonferroni-based tree gatekeeping strategy. [32, 33] Null hypotheses with adjusted p-values ≤ 0.05 will be rejected. 95% confidence intervals will be constructed around the treatment differences using asymptotic normal approximations. As a supportive analysis, these endpoints will be tested using the asymptotic Cochran Mantel-Haenszel statistic adjusting for site. Supportive analyses of the primary analysis will be repeated on the per-protocol (PP) set. **Analysis of Secondary Efficacy Endpoints** Analyses of secondary efficacy endpoints will be based on the ITT population. Missing data from subjects who are rescued or have discontinued the study prior to a study visit will be handled by either of two approaches: 1) missing data are imputed as failures; or 2) the last observation prior to the rescue medication or subject discontinuation is carried forward to subsequent visits (LOCF). With the exception of change from baseline to each follow-up visit, each of the secondary efficacy endpoints will be independently tested at each visit using similar statistical methods employed for primary efficacy endpoints (without the p-value adjustments).

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	Change from baseline (Visit 3) in AC cells and flare composite score (Anterior Chamber Reaction), as well as individual cells and flare scores, will be analyzed using both continuous and discrete statistical methods by treatment and visit, with missing data imputed by LOCF. Analysis of complete resolution of AC cells, and Grade 0 pain at each visit will be conducted using a Pearson Chi-squared test, with missing data imputed as failures, and also with missing data imputed by LOCF. Similar analyses will be performed for complete resolution of AC cells and flare combined and for flare separately. Other secondary or exploratory efficacy analyses may also be carried out as described in the study Statistical Analysis Plan. **Safety Endpoints** Tolerability endpoints will be summarized using discrete summary statistics by visit and treatment group. Treatment-emergent AEs (TEAEs), defined as AEs that occur after the first dose of study medication, will be summarized prior to and after rescue medication and as ocular and non-ocular events separately. Ocular events will be summarized for treated eyes and fellow eyes separately. Non-treatment-emergent events will be presented only in the listings, with ocular and non-ocular events displayed separately. A 95% confidence interval around the difference between treatment groups in the incidence of treatment-emergent AEs >1% will be constructed using asymptotic normal approximations. **Biomicroscopy and Fundoscopy** Biomicroscopy findings will be summarized at each visit and at the worst case on treatment by subject and parameter, both prior to and after rescue medication use. Incidence of treatment-emergent events will be tested using both a Pearson Chi-squared test and a Cochran Mantel-Haenszel test Fundoscopy measures will be summarized for screening and at Visit 6 (Postoperative Day 15) or upon study exit for early termination, for all subjects and subjects that had no rescue medication use. Incidence of treatment-emergent events will be tested using a Pearson Chi-squared test and a Cochran Mantel-Haenszel test adjusted for study sites. **Visual Acuity** Pinhole Snellen VA will be summarized at each visit as a categorical variable (20/20, 20/40, etc) and as a line change from baseline (Visit 3). Worst line change from baseline will also be presented. Visual acuity will be presented prior to and after rescue medication use. Subjects presenting a line change of >2 lines will be tested using a Pearson Chi-squared test and a Cochran Mantel-Haenszel test adjusted for study sites. **IOP** Intraocular pressure will be summarized at each visit and worst case on treatment for each subject using both continuous summaries (including change from baseline [Visit 3]) and discrete summaries. Results prior to and after rescue medication use will be presented separately. Discrete summaries will include: • The proportion of subjects with change in IOP from screening at any visit ≥5 and ≥10 mm Hg • The proportion of subjects with change in IOP from baseline at any visit

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	(Visit 3) ≥5 and ≥10 mm Hg • The proportion of subjects with treatment-emergent IOP ≥30 mm Hg • IOP at each visit categorized into: ≤5, 6 to 14, 15 to 21, 22 to 29, and ≥30 • Change from screening in IOP at each visit categorized into: ≤-5, -4 to 0, 1 to 4, 5 to 9, 10 to 14, and ≥15 • Change from baseline (Visit 3) in IOP at each visit categorized into: ≤-5, -4 to 0, 1 to 4, 5 to 9, 10 to 14, and ≥15 **Ocular Symptoms and Study Drug Sensation** Ocular symptoms will be summarized at each visit and presented by treatment separately for data obtained prior to receiving rescue medication and for data obtained after receiving rescue medication. Study drug sensation data collected at Visit 5 (Postoperative Day 8) will be summarized by treatment group. Tolerability endpoint analyses will use the Safety population with actual treatment received.

1.0 INTRODUCTION

Topical corticosteroids are useful in a variety of ophthalmic conditions and are generally indicated for treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.[1] Although corticosteroids are widely used as topical agents for ocular inflammation, most possess a risk profile that limits their general utility. A common risk associated with corticosteroid therapy is an elevation of intraocular pressure (IOP).[1, 2, 3] Additionally, steroids may result in the development of cataracts or may increase susceptibility to bacterial and fungal infection. [1, 4, 5]

Loteprednol etabonate (LE) is a co rticosteroid that has been designed according to the 'retrometabolic design' concept. [6, 7] Such drugs are designed to provide maximal therapeutic effects with minimal side effects. [8, 9] This goal is achieved by synthesizing the drug from a known inactive metabolite of a known active drug. The inactive metabolite is then structurally modified to an active form that will undergo a predictable 1-step transformation back to the inactive metabolite *in vivo*. [6, 7] Loteprednol etabonate is the 17B-chloromethyl ester of Δ^1 -cortienic acid, an inactive metabolite of prednisolone. [10]

Loteprednol etabonate exerts ocular anti-inflammatory effects when applied topically and undergoes a predictable metabolic deactivation process by enzymes that are found both in the eye and systemic circulation.[10] This rapid metabolism reduces the propensity of LE to elevate IOP because the inactive metabolites of LE are unable to interact with the glucocorticoid receptor, through which corticosteroid effects on IOP are mediated.

Loteprednol etabonate has been approved by the United States (US) Food and Drug Administration (FDA) as well as other global health authorities both as a single agent drug and as a fixed combination suspension for several clinical indications (cf, Lotemax® [loteprednol etabonate ophthalmic suspension, 0.5%], Lotemax® [loteprednol etabonate ophthalmic gel, 0.5%]), Alrex® [loteprednol etabonate ophthalmic suspension, 0.2%], Zylet® [loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension], and Lotemax® ointment [loteprednol etabonate ophthalmic ointment, 0.5%]). Clinical trial data have confirmed that the ophthalmic suspensions are well-tolerated by the eye and are efficacious in treating ocular inflammation. Loteprednol etabonate ophthalmic suspensions, in various concentrations, have been proven effective in several indications, including seasonal allergic conjunctivitis,[9, 11-14] giant papillary conjunctivitis,[15-17] uveitis,[18] and postoperative inflammation.[19, 20] Additionally, in clinical studies, LE ophthalmic suspension, 0.5% (Lotemax) has been shown to have a decreased incidence of significant IOP increase compared to prednisolone acetate. [21, 22] Thus, LE may offer a therapeutic advantage over conventional steroids by providing efficacy while reducing the risk for steroid-induced elevation of IOP.

Bausch + Lomb has formulated LE into a gel (loteprednol etabonate ophthalmic gel, 0.5% [Lotemax® gel, 0.5%]), a non-settling formulation which affords uniform distribution of the drug throughout the product. At room temperature and under low shear, the product behaves like a gel. [23] The gel formulation converts to a fluid under the shear forces experienced upon s queezing through the tip of the dispenser bottle. Following dosing, the contents of the bottle immediately reestablish the gel structure while the electrolytes in the tear fluid inhibit reformation of the gel

structure on the surface of the eye. Lotemax® gel 0.5% therefore yields a consistent dose to the patient without the need to shake the bottle and is formulated to have a more neutral pH than Lotemax® suspension. Additionally, during the development of the Lotemax® gel 0.5% formulation, it was determined that the level of benzalkonium chloride (BAK) required to provide preservative effectiveness in this formulation (30 ppm) was well below that typically used in ophthalmic products, including Lotemax® suspension (100 ppm). This reduced level of BAK is expected to improve tolerability of the gel formulation. Lotemax® gel, 0.5% is approved for the treatment of post-operative inflammation and pain following ocular surgery. Clinical trial data have confirmed that this gel formulation is well-tolerated and efficacious in treating postoperative inflammation. [24, 25]

Bausch + Lomb has recently developed an improved ophthalmic formulation of LE, loteprednol etabonate ophthalmic gel, 0.38% (LE gel 0.38%) in which the particle size of the drug is smaller (in the submicron range). The smaller particle size in the gel formulation serves to increase ocular penetration and residence time in anterior segment tissues while retaining many of the advantages of the current LE gel, 0.5% formulation. An ocular PK study conducted in rabbits (Bausch + Lomb study BL13001) demonstrated that the new, lower concentration (0.38%) formulation provides similar or greater exposure to LE in anterior segment tissues compared to Lotemax® gel, 0.5%.[26] In a separate study (Bausch + Lomb study 2013-GMP-042), systemic exposure to LE was evaluated in rabbits following ocular administration of LE gel, 0.38%. While the results of this investigation indicated that systemic exposure to LE was greater with the 0.38% LE gel formulation compared to Lotemax gel, 0.5%, overall, systemic exposure was very low. These PK results suggest that LE gel 0.38% is likely to be effective at treating ocular inflammation while providing a similar safety profile as Lotemax gel, 0.5%. The possible greater risks associated with higher anterior ocular tissue concentrations of loteprednol have been addressed by conduct of a 28-day GLP rabbit toxicology study with LE gel 0.38% that has shown negligible local or systemic toxicology findings compared to placebo.[27] In addition, a human PK study is planned to asses the degree of systemic exposure to loteprednol from the newer LE gel 0.38% formulation.

Additionally, in the interest of potentially improving patient dosing compliance, dosing frequency is addressed in the present clinical study. Loteprednol etabonate gel, 0.5% is indicated for QID dosing and the rabbit PK results with LE gel 0.38% have suggested less frequent dosing (eg, BID or TID) may be adequate to confer clinical efficacy. The present clinical study consequently is designed to examine whether this supposition is true; ie, whether BID dosing and/or TID dosing of LE gel 0.38% may be effective in reducing post-cataract surgery inflammation and pain.

2.0 OBJECTIVE

The primary objective of this Phase 3 study is to evaluate the safety and efficacy of LE gel 0.38% (BID and TID) for the treatment of postoperative inflammation and pain following cataract surgery.

3.0 STUDY DESIGN

3.1 Description of Study Design Including Choice of Control Groups

This is a multi-center, randomized, double-masked, vehicle-controlled study.

Subjects will be 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. Approximately 588 subjects will be randomized in a 2:2:1:1 ratio to LE gel 0.38% dosed TID, LE gel 0.38% dosed BID, vehicle dosed TID, or vehicle dosed BID. The 2 vehicle arms will be combined into 1 treatment group in the statistical analysis, and hence the study will have 3 treatment groups (ie, LE gel 0.38% TID, LE gel 0.38% BID, and [combined] vehicle groups). Each treatment group will consists of approximately 196 subjects.

Eligible subjects who are enrolled in the study will be seen for 7 scheduled study visits over the course of approximately 4 weeks. Treatment duration for this study will be approximately 14 days. Visit 1 shall occur no earlier than 14 days prior to surgery. The Visit 1 date will be the date on which the first Screening Assessment is performed and may or may not be the date on which the informed consent is obtained. Visit 2 will be on the day of surgery. At Visit 3 (Postoperative Day 1), eligibility for randomization into the study will be assessed. If eligible, subjects will be randomized and complete postoperative study Visits 4, 5, 6, and 7 (Postoperative Days 3, 8, 15, and 18, respectively).

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

3.2 Study Population

Approximately 588 subjects at up to approximately 60 investigative sites in the US who have undergone routine, uncomplicated cataract surgery will be enrolled in this clinical investigation.

3.2.1 Eligibility

3.2.1.1 Inclusion Criteria

To be enrolled in this study, each subject must:

Visit 1 (Screening) Criteria

1. Be 18 years or older on the date the Informed Consent Form (ICF) is signed and with the capacity to provide voluntary informed consent.
2. Be able to read, understand, and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF and provide Health Insurance Portability and Accountability Act (HIPAA) authorization.

3. Be willing and able to comply with all treatment and follow-up/study procedures.
4. Be 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, have 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 be postmenopausal at least 12 months prior to Visit 3 or permanently sterilized [eg, tubal occlusion, hysterectomy, bilateral salpingectomy])

     or
   - Have 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, agree to use adequate contraceptive methods prior to and during the study treatment period, as described below.
   - Female subjects of childbearing potential must use 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 is 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 use 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 use a condom with spermicidal foam/gel/film/ cream/suppository
8. Be willing to postpone cataract surgery on the fellow eye until after study completion.

Visit 3 (Postoperative Day 1) Criteria

9. Have undergone 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**
    - Not be of childbearing potential (female subjects not of childbearing potential must be postmenopausal at least 12 months prior to Visit 3 or permanently sterilized [eg, tubal occlusion, hysterectomy, bilateral salpingectomy])

      or

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

3.2.1.2 Exclusion Criteria

To be enrolled in this study, each subject must not:

1. Have a severe/serious ocular condition or history/presence of chronic generalized systemic disease that the Investigator feels might increase the risk to the subject or confound the result(s) of the study.
2. Be a female subject who is pregnant or breastfeeding.
3. Have ocular hypertension (IOP ≥ 21 mmHg), glaucoma, or any glaucoma-related incisional or laser surgery in the study eye. *Note: This exclusion criterion must apply to both Visit 1 (Screening) and Visit 3 (Postoperative Day 1).*
4. Be monocular (fellow eye is nonfunctional or fellow eye's pinhole vision is worse than Snellen 20/200).
5. Have 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. Have a current diagnosis of cystoid macular edema in the study eye.
7. Have any abnormality that prevents reliable Goldmann applanation tonometry in either eye.
8. Have iris atrophy in the operative eye.
9. Have lens pseudoexfoliation syndrome with glaucoma or zonular compromise in the study eye.
10. Be unable, for any reason, to discontinue contact lens use in the study eye during the course of the study.
11. Have 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. Have proliferative diabetic retinopathy or moderate to severe non-proliferative diabetic retinopathy in the study eye.
13. Have 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. Have a congenital ocular anomaly in either eye.
15. Have a presence of active external ocular disease: infection (bacterial, viral or fungal) or inflammation (including allergic) of the study eye.
16. Have used ocular therapy (either eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), mast cell stabilizers, antihistamines, or decongestants within 2 days prior to surgery or be expected to require any of these treatments during the 18 days following cataract surgery.
17. Be expected to require treatment with systemic NSAIDs, antihistamines, or decongestants during the 18 days following cataract surgery with the exception of $\leq$ 81 mg/day of acetylsalicylic acid.
18. Be expected to require treatment with any systemic, inhaled, nasal, or ocular (either eye) corticosteroids or glucocorticoids during the 18 days following cataract surgery or have used any systemic or ocular corticosteroids within 14 days prior to cataract surgery. Dermal use outside the ocular area is permitted.
19. Be expected to require concurrent systemic or ocular therapy with immunosuppressants (eg, Restasis) during the 18 days following cataract surgery or have used ocular immunosuppressants within 30 days prior to surgery.
20. Have known hypersensitivity or contraindication to the study drug(s) or their components.
21. Have 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. Have been previously randomized in this study.
23. Currently require or be expected to require treatment with any medication listed as a disallowed medication per the Disallowed Therapy Section of this protocol.

3.3 Investigators

This study will be conducted at up to approximately 60 investigative sites located in the US and will have competitive subject enrollment.

This study will be conducted by Investigators who are determined by Bausch + Lomb to be suitably qualified by training and experience to conduct this study in compliance with all applicable GCPs and FDA Federal Regulations or Local Regulations. Sub-Investigators will be identified on the FDA Form 1572.

3.4 Study Duration

Eligible subjects who are enrolled in the study will be seen for 7 scheduled study visits over the course of approximately 4 weeks. Treatment duration with study drug for this study will be approximately 14 days, starting at Visit 3 (Postoperative Day 1) and ending on the evening before Visit 6 (Postoperative Day 15).

3.5 Treatments

There will be 2 treatments in this study: LE gel 0.38% (loteprednol etabonate ophthalmic gel, 0.38%) and the vehicle of LE gel 0.38%. Additionally, there will be 2 dosing regimens assessed in this study: BID and TID. Subjects will be randomized in a 2:2:1:1 ratio to LE gel 0.38% dosed TID, LE gel 0.38% dosed BID, vehicle dosed TID, and vehicle dosed BID according to a computer-generated randomization list. Subjects randomized to BID groups will instill 1 drop of study drug into the study eye, 2 times per day at approximately 12 hour intervals. Subjects randomized to TID groups will instill 1 drop of study drug into the study eye, 3 times per day at approximately 8 hour intervals. All subjects will administer study treatment for approximately 14 days.

3.6 Selection of Dose

The concentration of LE gel 0.38% was selected for investigation based on modeling of data from preclinical studies conducted with previously approved ophthalmic formulations of LE and a recent rabbit PK study conducted by Bausch + Lomb.[26, 28-31] The dose regimens and dosing duration being tested in this clinical study (1 drop of study drug instilled either BID or TID) for 14 days was selected based on the standard of care for post-operative pharmacologic management of cataract surgery patients and ocular pharmacokinetic and pharmacodynamic modeling of LE gel 0.38%.

4.0 STUDY MATERIALS

4.1 Description of Investigational Product

The test article, LE gel 0.38%, contains the active ingredient loteprednol etabonate, 0.38%, and the preservative benzalkonium chloride, 0.003%. It also contains the inactive ingredients boric acid, edetate disodium dihydrate, glycerin, hypromellose, poloxamer 407, polycarbophil, propylene glycol, sodium chloride, sodium hydroxide, and water for injection.

4.2 Description of Comparator Product

The comparator, vehicle of LE gel 0.38%, contains the preservative benzalkonium chloride 0.003% and the inactive ingredients boric acid, edetate disodium dihydrate, glycerin, hypromellose, poloxamer 407, polycarbophil, propylene glycol, sodium chloride, sodium hydroxide, and water for injection.

4.3 Instructions for Use and Administration

Subjects will be instructed on the proper use, administration, and storage of their study drug, as well as use of a subject dosing diary.

Subjects will be instructed to invert the closed study drug bottle and shake once to fill the bottle tip before the initial use. Subjects will be instructed to instill 1 drop of study drug into the conjunctival sac of the study eye according to the dosing schedule to which they were randomized.

Assignment of BID dosing or TID dosing for a subject will be determined by a computer-generated randomization list (see Section 4.7.1). Each kit box will include a masked dosing envelope that will contain administration instructions for either BID or TID dosing, in accordance with the subject's randomization assignment. For BID dosing, subjects will be instructed to administer 1 drop of study drug in the study eye 2 times per day, at approximately 12 hour intervals. For TID dosing, subjects will be instructed to administer 1 drop of study drug in the study eye 3 times per day, at approximately 8 hour intervals. All subjects will dose for approximately 14 days. The first dose will be administered in the clinic at Visit 3 (Postoperative Day 1) and the last dose will be administered on the evening before Visit 6 (Postoperative Day 15).

Subjects will be instructed regarding proper study drug storage, as described below (Section 4.3.1).

Subjects will be given diaries to record each study drug instillation during the treatment period. Study personnel will instruct the subjects to bring the diary to each of their follow-up visits and remind subjects that no other information should be recorded in the diary.

4.3.1 Storage Requirements

All study drug must be stored upright in an area free from environmental extremes and protected from light, at controlled room temperatures between 59-77°F (15-25°C) as specified on the study drug label. The storage location at the clinical site must have limited access and be available only to unmasked study site personnel.

4.4 Packaging and Labeling

The study drugs will be packaged and labeled in a manner consistent with the study design and according to a computer-generated randomization scheme. For masking purposes, both the investigational product and comparator product will be manufactured and filled (5 g) into 10 mL, white, low density polyethylene (LDPE) plastic bottles with pink polypropylene caps by Bausch + Lomb (Tampa, FL). All study material will be similarly labeled by Bausch + Lomb (Rochester, NY).

Subject supplies will be labeled according to a computer-generated randomization scheme. The medication will be identified as a new drug and appropriately labeled for investigational use. Supply labeling will minimally include:

- Protocol number

- Kit identification number
- Product description
- Directions for use
- Storage conditions
- Caution statement
- Sponsor information

Study drug bottles will be provided in cardboard kit boxes. One kit box will be provided for each subject. The kit box will be dispensed at Visit 3 (Postoperative Day 1) and will contain 2 identical investigational product (IP) bottles.

Subject kit boxes will have attached a 2-part, peel-off label. The left part of the label will remain affixed to the subject kit. Upon dispensing, the right portion of the label will be detached and placed on a printed label page in the Master Medication Log provided by the Sponsor. The Master Medication Log will be kept in the site Regulatory Binder maintained by the Investigator or designee.

4.5 Accountability

The Investigator or designee will be responsible for keeping current and accurate records of the amount of study drug received and dispensed, and its disposition. The study drug must be stored under the appropriate conditions in a secure area and is to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator or designee must maintain an inventory of all study drug dispensed to or returned by the subject, including subject identifiers.

In order to assess compliance of administration, subjects will be instructed to record the date and time of each study drug administration on a diary provided by the Sponsor. Subjects should bring their study drug and study drug administration diary to Visits 4 through 6.

At time points throughout the study and/or upon completion of the study, a representative from Bausch + Lomb will review and verify the Investigator's accountability records. Following verification, and as directed by Bausch + Lomb, all used and unused product must be returned to the Bausch + Lomb at the address listed on the Personnel and Facilities Page, or with the Sponsor's permission, disposed of at the site in an appropriate manner.

All kits shipped to sites will need to be confirmed within the Interactive Web Response System (IWRS) as being received in 'Good' or 'Damaged' condition. Kits received in 'Good' condition will be available for dispensation to subjects.

4.6 Masking/Unmasking

This study is double-masked; therefore, the Investigator/site staff, subjects, and Bausch + Lomb personnel or designee(s) involved in the conduct or monitoring of this study will be masked to the study treatment (LE gel 0.38% or vehicle) for the duration of the study. The treatment

randomization list will be produced prior to commencement of the study by an unmasked statistician not otherwise involved in the conduct or monitoring of the study.

In addition to the masking noted above, the Investigator and other site personnel responsible for assessing safety and/or efficacy measures, also will be masked to the frequency of study drug dosing (either TID or BID) assigned to subjects. At least 1 prospectively identified designee at each site who is not involved in assessing safety or efficacy of the study drug will be unmasked to the frequency of study drug dosing assigned to subjects. The unmasked designee(s) will be responsible for receipt, storage and dispensing of study drug, and will be listed on the Delegation of Authority Log as having these responsibilities. The designee(s) will also be responsible for insuring subjects are receiving appropriately consistent study materials (study drug and use instructions), training subjects on the use of study drug, witnessing the first use of the study drug at Visit 3, and collecting/reviewing study drug administration diaries at each visit for accuracy and compliance. To ensure maintenance of masking, Investigators and other study personnel masked to the frequency of study drug dosing must not be present during any in-office study drug instillations, nor should they be present for study diary reviews by the unmasked designee. Additionally, subjects will be instructed to keep their study drug bottles inside of the outer cardboard kit boxes during office visits, not to reveal their study drug or study diaries to the Investigator(s) and other masked study personnel. Subjects should also refrain from discussions regarding study drug with the Investigator(s)/masked study personnel as well as other study participants.

In an emergency situation where knowledge of the study treatment is critical to subject safety, the study treatment for that subject can be unmasked through the IWRS. During unmasking the IWRS provides both the treatment assignment of the randomization schedule assignment and the treatment of the kit assigned to the subject. Under normal circumstances, masking should not be broken. Should the masking need to be broken, the Investigator must contact the Medical Monitor prior to unmasking of study treatment. The Investigator should make every effort to obtain approval from the Medical Monitor for unmasking a subject's randomization code before acting unilaterally. In an emergency situation, however, where knowledge of the study treatment is critical to subject safety, the randomization code may be broken without prior Medical Monitor approval. In such cases, the Investigator must notify the Medical Monitor and/or Bausch + Lomb Study Manager as soon as possible after unmasking a subject's treatment allocation. In addition, the Investigator must record the date, time, and reason for unmasking the study drug treatment in the source documentation, and the appropriate form located in the Regulatory Binder. Individual unmasking by the Investigator will normally result in withdrawal of the subject from the study and should only be performed for the specific subject requiring unmasking of their treatment group.

4.7 Methods of Assigning Subjects to Treatment Groups

4.7.1 Randomization

Prior to study enrollment a computer-generated randomized list of study drug numbers and corresponding drug treatments will be produced by an unmasked statistician who is not otherwise involved in the study. Each kit number will correspond to a study drug treatment (LE

gel 0.38% dosed TID, LE gel 0.38% dosed BID, vehicle dosed TID, or vehicle dosed BID). Each kit number will be used to label a kit and its corresponding 2 drug bottles. Instructions appropriate for the dosing frequency will be stored in envelopes within each kit box and correspond to the kits designated treatment type. As noted above (Section 4.6), only the subject and designated staff will be unmasked to the dosing frequency.

4.7.2 Treatment Allocation

At Visit 3, subjects who meet all inclusion and none of the exclusion criteria will be randomized in a 2:2:1:1 ratio to receive LE gel 0.38% dosed TID, LE gel 0.38% dosed BID, vehicle dosed TID, or vehicle dosed BID. Allocation of study drug will be completed through the use of an IWRS. Site personnel will use the IWRS to retrieve a kit number assignment for subjects who are found eligible for enrollment at Visit 3. Site personnel will be responsible for dispensing and collecting the appropriate study drug and kit box to and from the study subjects.

4.7.3 Treatment Replacement

In the event that a subject's kit box is lost, damaged, or depleted prior to the end of treatment, the Unmasked Designee will use the IWRS to retrieve a kit box number for a replacement kit box to be dispensed to the subject from the supplies available at the site. The IWRS will identify a replacement kit box that matches the subject's treatment assignment and will assign the kit to the subject. Separate reserve supplies will not be provided to the site. Treatment replacement is allowed as long as the subject does not miss more than 1 planned dosing.

4.8 Other Study Materials

Additional materials provided by the Sponsor include the following:

- Urine pregnancy test kits
- Min/max room thermometers, if necessary
- Wratten gel filter

5.0 EFFICACY AND SAFETY VARIABLES

5.1 Efficacy Variables

Efficacy assessments will include the following:

- AC cells (by Investigator)
- AC flare (by Investigator)
- Ocular pain (by subject)

See Appendix B for details on the efficacy assessment procedures and grading scales.

5.2 Safety Variables

Safety assessments by the Investigator will include the following:

- Ocular and non-ocular AEs
- IOP
- Ocular signs (biomicroscopy)
  - Slit lamp examination of ciliary flush, conjunctival chemosis, eyelid erythema, conjunctival injection, corneal staining, corneal edema, hyphema, posterior synechiae, anterior vitreous haze, precipitates, hypopyon
- VA
- Ophthalmoscopy
  - Dilated fundus examination of retina, macula, choroid, optic nerve, and cup/disc ratio

See Appendix B for details on the safety assessment procedures.

5.3 Tolerability Variables

Tolerability assessments by each subject will include the following:

- Study drug sensation assessment at Visit 5 (Postoperative Day 8)
- Ocular symptoms
  - Photophobia, itching, tearing, and discharge

See Appendix B for details on the tolerability assessment procedures and grading scales.

5.4 Appropriateness of Variables

In this study, all assessments and evaluations to assess the efficacy and safety of LE gel 0.38% are considered standard practice in the field of ophthalmology for diagnosis and management of postoperative inflammation and pain following routine cataract surgery.

5.5 Risk Assessment

The subjects will be informed of any risks in the ICF. If additional risks are identified, the Sponsor will notify the Investigators.

6.0 STUDY METHODS

The following assessments must be performed by an ophthalmologist as required at a given study visit:

- Elicitation and recording of AEs (ophthalmologist or qualified designee (eg, sub-investigator)
- Slit-lamp examination (biomicroscopy)
- Dilated ophthalmoscopy

- IOP assessments

6.1 Study Visits

Refer to Appendix A for a schedule of visits and parameters and Appendix B for methods of clinical evaluation.

Following identification of a potential subject, the Investigator or designee will explain the purpose of the study, procedures, risks/benefits, and subject responsibilities to the potential subject. The subject's willingness and ability to meet the follow-up requirements of the study will be determined. If the subject chooses to participate in the investigation, written informed consent will be obtained. The subject and the person obtaining written consent will sign and date the IRB-approved ICF. At the point of signing the ICF, the subject is considered part of the study population. The original signed document(s) will be retained in the subject records, and a copy will be provided to the subject. In addition, HIPAA authorization must be obtained from each subject.

6.1.1 Visit 1: Screening Assessment

NOTE: Visit 1 shall occur no earlier than 14 das prior to surgery. The Visit 1 date will be the date on which the first screening assessment is performed The informed consent date may be the same as or prior to visit 1(screening assessent date).

- Obtain written informed consent and HIPAA authorization
- Determine if the subject meets preliminary eligibility criteria
  - Collect demographic information
  - Collect current and relevant medical and ophthalmic history
  - Identify concomitant medications used
  - Perform a urine pregnancy test, as applicable
- If the subject meets the preliminary eligibility criteria, the following assessments will be performed:
  - Perform a clinical assessment of ocular symptoms
  - Perform assessment of pin-holed Snellen VA
  - Perform biomicroscopy assessments
  - Perform IOP measurement (measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy)
  - Perform dilated fundus examination
- Collect and record AEs

NOTE: Surgery will be scheduled to occur ≤ 14 days of the first ScreeningAssessment Visit. Screening and surgery cannot take place on the same day.

6.1.2 Visit 2: Surgery (≤ 14 days of Visit 1/first Screening Assessment performed)

The following must be performed prior to the surgery:

- Collect and record AEs and changes in concomitant medications.

NOTE: Following surgery, subjects may only receive antibiotics and will be scheduled to return in 18 to 34 hours to determine if they have sufficient ocular inflammation to be included in the study (see Inclusion Criterion #12). Subjects who do not receive a posterior chamber IOL or who, in the Investigator's opinion, have complications such that it is not in the subject's best interests to continue in the study are to be considered screen failures.

NOTE: If during the surgery it is determined that additional manipulations, such as pupil stretching or the use of iris hooks or peripheral relaxing corneal incisions are required, the subject is not eligible to participate in the trial.

6.1.3 Visit 3: Postoperative Day 1 (Randomization [18 to 34 hours post-surgery])

NOTE: Post-surgery visits should be scheduled so that IOP can be assessed within ± 2 hours of the time of IOP assessment on Visit 1.

- Perform a urine pregnancy test, as applicable
- Perform a clinical assessment of ocular symptoms
- Perform assessment of pin-holed Snellen VA
- Perform biomicroscopy assessments
  - Assess AC cells (refer to Appendix B)
    - If the AC cell grade is ≥ 2, then the subject is eligible and will be randomized.
    - If the AC cell grade is < 2, then the subject is not eligible and will be a screen failure.
- Perform IOP measurement
  - IOP should be assessed within ± 2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy.
  - If a one-time intervention is necessary to reduce IOP prior to randomization (eg, 'burping' the paracentesis, Diamox, or topical hypotensive agent) and the pressure returns to normal, the subject can be randomized into the study. The AE and intervention should be recorded on the appropriate logs (eg, Adverse Event, Concomitant Medication, and Ocular Surgical Intervention) and the final IOP measured prior to randomization should be recorded in the eCRF.
- Randomize eligible subjects by assigning the next applicable subject kit number
- Dispense study drug kit to the subject

- Instruct the subject to instill 1 dr op of study drug into the study eye according to the instructions provided with the kit.
  - Subjects should instill their initial dose while in the clinic to ensure that they understand and are able to follow instructions for instillation.
  - The Investigator and study staff involved in assessments of safety and efficacy must not be present during the in-office study drug instillation.
  - Remind subjects to instill all doses on Day 1 even if the interval between doses is shorter than described in the kit instructions.
  - For those subjects receiving a topical antibiotic, remind the subject that the topical antibiotic drops must be instilled a minimum of 15 minutes BEFORE study drug application.
- Collect and record AEs and changes in concomitant medications
- Provide a Study Drug Administration Diary to the subject. Instruct the subject to record each instillation in the diary and to bring the diary and study drug (all bottles) to the next visit. Remind the subject that no other information should be recorded in the diary.

6.1.4 Visit 4: Postoperative Day 3 (± 1 Day)

NOTE: Post-surgery visits should be scheduled so that IOP can be assessed within ± 2 hours of the time of IOP assessment on Visit 1.

- Perform a clinical assessment of ocular symptoms
- Perform assessment of pin-holed Snellen VA
- Perform biomicroscopy assessment
- Perform IOP measurement
  - IOP should be assessed within ± 2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy.
- Collect and record AEs and changes in concomitant medications
- Collect and review the Study Drug Administration Diary for accuracy and compliance. Dispense a new Study Drug Administration Diary. Instruct the subject to record the time of each instillation in the diary and to bring the diary and study drug (all bottles) to the next visit. Remind the subject that no other information should be recorded on the diary.
- Remind the subject to instill 1 drop of study drug into the study eye according to the instructions provided with the kit. For those subjects receiving a topical antibiotic, remind the subject that the topical antibiotic drops must be instilled a minimum of 15 minutes BEFORE study drug application.

NOTE: Subjects will be assessed at Visits 4 through 7 (Postoperative Days 3, 8, 15, and 18) for treatment rescue. Subjects with worsening or no change in the grade of inflammation in the study eye compared with the previous visit are eligible and may be considered for rescue medication at the discretion of the Investigator. The choice of rescue medication and dosing shall be determined by the Investigator. See Section 6.2.3.1 for more details.

6.1.5 Visit 5: Postoperative Day 8 (± 1 Day)

NOTE: Post-surgery visits should be scheduled so that IOP can be assessed within ± 2 hours of the time of IOP assessment on Visit 1.

- Perform a clinical assessment of ocular symptoms
- Perform study drug sensation assessment
- Perform assessment of pin-holed Snellen VA
- Perform biomicroscopy assessment
- Perform IOP measurement
  - IOP should be assessed within ± 2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy.
- Collect AEs and changes in concomitant medications
- Collect and review the Study Drug Administration Diary for accuracy and compliance. Dispense a new Study Drug Administration Diary. Instruct the subject to record the time of each instillation in the diary and to bring the diary and study drug (both bottles) to the next visit. Remind the subject that no other information should be recorded on the diary.
- Remind the subject to instill 1 drop of study drug into the study eye according to the instructions provided with the kit. For those subjects receiving a topical antibiotic, remind the subject that the topical antibiotic drops must be instilled a minimum of 15 minutes BEFORE study drug application
- Remind the subject that the last instillation of study drug will occur the evening before Visit 6. If the subject doses on the day of Visit 6 the visit should be performed as scheduled.

6.1.6 Visit 6: Postoperative Day 15 (± 1 Day) (End of Treatment Period)

NOTE: Post-surgery visits should be scheduled so that IOP can be assessed within ± 2 hours of the time of IOP assessment on Visit 1.

- Perform a clinical assessment of ocular symptoms
- Perform assessment of pin-holed Snellen VA
- Perform biomicroscopy assessment

- Perform IOP measurement
  - IOP should be assessed within ± 2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy.
- Perform dilated fundus examination
- Collect and record AEs and changes in concomitant medications
- Collect and review the Study Drug Administration Diary for accuracy and compliance
- Collect all used and unused study drug (all bottles) from the subject

6.1.7 Visit 7: Postoperative Day 18 (± 1 Day) (Post-treatment exam)

NOTE: Post-surgery visits should be scheduled so that IOP can be assessed within ± 2 hours of the time of IOP assessment on Visit 1.

- Perform a urine pregnancy test, as applicable
- Perform a clinical assessment of ocular symptoms
- Perform assessment of pin-holed Snellen VA
- Perform biomicroscopy assessment
- Perform IOP measurement
  - IOP should be assessed within ± 2 hours of the time IOP was assessed at Visit 1 (Screening). Measurement of IOP must occur after the assessment of ocular symptoms and biomicroscopy.
- Collect AEs and changes in concomitant medications
- Exit the subject from the study

6.1.8 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

If a subject is seen for multiple visits within a given visit timeframe, the data from the visit that are intended to meet protocol requirements for the scheduled visit should be captured on the visit eCRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol-required scheduled visit eCRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit eCRF.

6.1.9 Missed Visits

If a subject misses any scheduled follow-up visit and cannot be seen prior to the start of the allowed visit range for the next scheduled follow-up visit, the visit is considered missed.

6.2 Study Completion

Bausch + Lomb Clinical Operations will notify the Investigator of when to contact the IRB/EC to inform them that the study is complete.

6.2.1 Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigator(s), IRB, and FDA. Bausch + Lomb will instruct the Investigators to stop dispensing study materials and to arrange for study closeout at each site.

6.2.2 Subject Completion

A subject has completed the study when Visit 7 has been completed and the subject has been exited. Subjects who require further follow-up for an AE will be followed according to Sections 7.3 and 7.4.

NOTE: If rescue is required at Visit 7 and all assessments have been completed the subject has completed the study and can be exited.

6.2.3 Subject Discontinuation

A subject MAY be discontinued (at the discretion of the Investigator, the Sponsor and/or the IRB/EC) prior to the final study visit for several reasons, including, but not limited to:

- A serious adverse event (SAE) occurring during the course of the study, which precludes continued treatment or follow-up
- The subject not following required study procedures
- If a subject exhibits intolerable adverse events (AEs, related or not related to the study treatment), or if a subject fails to show improvement in inflammation or the clinical status of inflammation worsens, the treating Investigator may opt to withdraw the subject from the trial and implement necessary intervention (ie, rescue therapy)

A subject MUST be discontinued prior to the final study visit for any of the following reasons:

- Voluntary withdrawal
- Death
- Pregnancy
- Rescue Medication
- Investigator decision that it is not in the best medical interests of the subject to continue participation in the investigation

Prior to discontinuing a subject, every effort should be made to contact the subject, schedule a final study visit (see Appendix A, Early Discontinuation visit), obtain as much follow-up data as possible, and to retrieve all study materials. Adverse events will be followed as described in Sections 7.3 and 7.4. An early termination visit should take place within 7 days following the subject being discontinued. If a subject is discontinued during a given scheduled visit, the early termination procedures as outlined in Appendix A may be performed at that visit. Subject withdrawals will be documented clearly on the source document and applicable electronic case report form (eCRF).

Notification of subject discontinuations will be made to the Sponsor. Any subject discontinued from the study will not be replaced.

6.2.3.1 Rescue Medication

Subjects will be assessed at Visits 4 through 7 (Postoperative Days 3, 8, 15, and 18) for treatment rescue. Subjects with worsening or no change in the grade of inflammation in the study eye compared with the previous visit are eligible and may be considered for rescue medication. For subjects who meet either of these criteria, it is at the discretion of the Investigator when to begin rescue medication. The choice of rescue medication and dosing shall also be determined by the Investigator. Subjects requiring rescue medication for inflammation will stop treatment with the study drug and will be promptly discontinued from the study. The inflammation will not be reported as an adverse event (AE). The rescue medication will be recorded on the Concomitant Medication electronic case report form (eCRF) and the exit reason will be entered as “rescue medication” in the eCRF. Subjects who receive rescue medication will be counted as treatment failures as of the date of receiving rescue medication. Subjects who require rescue medication should return within 7 days following the date that rescue medication begins in order to undergo the procedures for the early termination visit.

NOTE: Rescue med that is required at V7 will not be recorded on the ConMed eCRF

6.2.4 Lost to Follow-up

Subjects who do not return for scheduled follow-up visits, as defined by the visit window, and who cannot be contacted after at least 2 attempts may be considered lost to follow-up. All follow-up attempts will be documented and kept with the subject’s source documentation, and the applicable eCRFs will be completed.

6.3 Concomitant Medications/Therapy

Administration of all medications used up to 30 days prior to study entry (ie, date ICF signed) through study exit must be recorded in the source documentation and in the appropriate section of the Concomitant Medications eCRF. Indications for these medications should be recorded in the subject's Medical History eCRF or Adverse Event eCRF, as applicable. Medication used intraoperatively will be recorded only in source documentation (also refer to Section 6.3.1).

6.3.1 Permitted Therapy

With the exception of the disallowed medications specified in the eligibility criteria (Section 3.2.1) and in Section 6.3.2, any medications that, in the Investigator's judgment, will not interfere with the study parameters are allowed to be used concurrently. For example, the following medications listed in Table 1 are permitted:

Table 1: Permitted Therapies

Medication/Class of Drug	Status
Acetaminophen	Permitted
Acetylsalicylic Acid ≤ 81 mg/day	Permitted
Anesthetic Agents [a]	Permitted for surgery, IOP, and fundus examination ONLY
Antibiotic, Intracameral Injection at end of surgery [b]	Permitted
Antibiotic, Topical (NOT combined with a steroid) [c]	Permitted
Anti-Cholesterol Medications	Permitted
Antidepressants	Permitted
Antihypertensive Agents	Permitted
Antimicrobials, Systemic	Permitted
Birth Control Pills	Permitted
Cardiovascular Agents	Permitted
Epinephrine/Noradrenaline	Permitted for surgery ONLY
Estrogen Therapy	Permitted
Oral Histamine H_2 Receptor Antagonist (example: Zantac)	Permitted
Hypoglycemic Agents	Permitted
Hypotensive Medication, topical ocular	Permitted for one-time use at Day 1 post-op (Visit 3)
Insulin	Permitted
Mydriatic Agents [a]	Permitted for surgery and fundus examination ONLY
Neosynephrine/Phenylephrine	Permitted for surgery and fundus examination ONLY
Thyroid Preparations	Permitted

[a] Standard anesthetic and mydriatic agents may be used intraoperatively and for IOP and fundus examination ONLY.
[b] Intracameral injection of antibiotic is allowed at the end of surgery.
[c] Use of topical antibiotics is allowed if they are not used in combination with any steroid (eg, Zylet® or TobraDex should not be used).

NOTE: Intraoperative use of topical antibiotics or other standard of care surgical medications should be recorded in the source documentation only. Topical antibiotics used preoperatively or postoperatively should be recorded in the Concomitant Medications eCRF provided by the Sponsor.

Subjects requiring post-surgical treatment rescue will be considered treatment failures and subjects will stop use of study drug. Document all rescue medication use in the eCRFs.

Please refer to Section 6.2.3.1 Rescue Medication on page 41 for Early Term Visit

6.3.2 Disallowed Therapy

A disallowed medication may be administered in an emergency if the subject's safety is in jeopardy. If possible, the Medical Monitor should be consulted prior to administration of the disallowed medication (if not feasible, then as soon as possible afterwards) to determine whether the subject may continue in the study.

If a subject has taken any disallowed medication for any reason other than rescue therapy, record this as a protocol deviation and immediately contact Bausch + Lomb.

Disallowed medications include, but are not limited to the following:

Table 2: Disallowed Therapies

Medication/Class of Drug	Status
Acetylsalicylic Acid > 81mg/day	Excluded starting 2 days before surgery and through 18 days after surgery
Antihistamines (H-1 Antagonist), systemic or ocular	Excluded starting 2 days before surgery and through 18 days after surgery
Artificial Tears	Excluded starting 7 days before surgery and through 18 days after surgery
Biologic Agents (example: anti-TNF-α [eg, Cimzia])	Excluded starting the day of surgery and through 18 days after surgery
Corticosteroids/Glucocorticoids: systemic, inhaled, or ocular	Excluded starting 14 days before surgery and through 18 days after surgery
Decongestants, systemic or ocular	Excluded starting 2 days before surgery and through 18 days after surgery
Flomax (tamsulosin)	Excluded starting 7 days before surgery and through 18 days after surgery
Hydrocodone/Opioid-Based Pain Medications	Excluded starting the day of surgery and through 18 days after surgery (can be used ONLY during surgery)
Ocular Hypotensive Medication, oral (eg, Diamox)	Excluded except for use during IOP one-time intervention at V3
Ocular Hypotensive Medication, topical (eg, Betaxolol)	Excluded except for use during IOP one-time intervention at V3
Immunosuppressants, systemic or ocular	Excluded starting 30 days before surgery and through 18 days after surgery
Mast cell Stabilizers, systemic or ocular	Excluded starting 2 days before surgery and through 18 days after surgery
Methotrexate/DMARDs	Excluded starting 30 days before surgery and through 18 days after surgery
NSAIDs and COX-2 Inhibitors, systemic or ocular	Excluded starting 2 days before surgery and through 18 days after surgery
Plaquinil/Anti-malarial drugs	Excluded starting 30 days before surgery and through 18 days after surgery
Propoxyphene	Excluded starting 2 days before surgery and through 18 days after surgery
Serratiopeptidase	Excluded starting 7 days before surgery and through 18 days after surgery

Abbreviations: COX, cyclooxygenase; DMARD, disease-modifying anti-rheumatic drugs; TNF, tumor necrosis factor.

Additionally, any medication the subject uses that the Investigator and/or Medical Monitor feels may interfere with subject safety or study parameters should be considered a disallowed medication.

Disallowed medication that is used for persistent or worsening inflammation is called "Rescue Medication" and is discussed in Section 6.2.3.1. Subjects taking rescue medication must stop

using the study drug and be withdrawn from study participation. Subjects requiring rescue medication will be considered treatment failures.

6.4 Treatment Compliance

Any subject who does not follow instructions to a degree that, in the opinion of the Sponsor or the Investigator, jeopardizes the subject's well-being or the validity of the study, must be discontinued.

Subjects will be given study drug administration diaries to record the date and time of each study medication instillation. Treatment compliance during the study will be documented by subject entries in the study diaries. Study personnel will instruct the subject to bring the study diary to each of their follow-up visit(s) and remind subjects that no i nformation other than dosing information should be recorded in the diary.

6.5 Protocol Deviations

Protocol deviations will be defined prior to first subject first visit (see Section 8.5.6). The IRB/EC definitions for protocol deviations will be assumed by inference to be part of this protocol, if available. The definition of protocol deviation severity may change during the study and all major protocol deviations will be identified prior to database lock.

The date and reason for any protocol deviation will be documented in all cases. Significant or major protocol deviations impacting the safety of the subject or the integrity of the study must be reported by the Investigator to the IRB/EC and the Sponsor immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB/EC.

Protocol deviation assessments will continue for all subjects until the end of the study, unless the protocol deviations put a subject at risk or the subject's condition requires that he/she be discontinued from the study.

7.0 ADVERSE EVENTS

7.1 Definition of Adverse Events

- Any untoward medical occurrence (including an abnormal laboratory finding) in a subject participating in a clinical study that does not necessarily have a causal relationship with the study protocol and/or procedure or with the study treatment.

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease with onset following the signing of informed consent through study exit, whether or not considered related to the study. An AE can also include a progression/worsening of underlying disease, hypersensitivity, and extravasation.

- Events occurring from drug overdose, whether accidental or intentional, events occurring from drug abuse, drug misuse, drug interactions, drug dependency, events occurring from drug withdrawal, and medication errors.

- A treatment-emergent AE (TEAE) is defined as an AE with a start date on or after the first dose of study drug, or that worsened following first administration of study drug.

7.2 Definition of Serious Adverse Events

Information about every serious adverse event (SAE) will be collected and recorded. An SAE is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Is sight-threatening (may result in persistent or significant loss of vision)
- Encompasses any medically significant event that may jeopardize a subject and may require medical or surgical intervention to prevent any of the outcomes listed above
- Is medically significant, as determined by the Principal Investigator or medically qualified Sub-Investigator

A medically significant event that does not result in any of the above may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize a subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Important medical events that may not have resulted in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Additionally, any suspected transmission of an infectious agent by a Bausch + Lomb product, pathogenic or non-pathogenic, is considered an SAE. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a Bausch + Lomb product. The terms “suspected transmission” and “transmission” are considered synonymous.

Hospitalization is a criterion for assessment of seriousness. To qualify as serious under the criteria of “hospitalization,” a hospital admission of at least a 24-hour period is required. If a

subject is retained the emergency room greater than 24 hours, but not admitted for medical care, these cases should be evaluated individually, as criteria such as "medically significant" may also apply.

Hospitalization without a medical AE should not be considered either serious, or an AE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Hospitalization for a purpose unrelated to the study (eg, "planned" or elective surgery scheduled prior to study participation) would not ordinarily need to be reported, unless a complication occurred which otherwise caused prolongation of this hospitalization.
- Protocol-specified admission or procedure (eg, cataract surgery required by a study protocol; or overnight stay for monitoring due to protocol required surgery, *with no associated SAE or complication necessitating prolonged stay*)
- Social admission (eg, social hospitalization for purposes of respite care)

7.3 Reporting Adverse Events and Follow-up

Throughout the course of the study, efforts will be made by the Investigator to remain alert to possible AEs that are either systemic or ocular in nature. The period of observation for collection of AEs extends from the time the subject gives informed consent until the last study visit or discontinuation from the study. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The Investigator or designee will elicit reports (ie, via direct questioning, observation, clinical evaluation) of AEs from the subject at each study visit and record all AEs. The Investigator will document the dates of onset, progress, outcome, and resolution of such AEs. The Investigator will also provide an assessment of all AEs as to the severity, causal relationship to study drug, and causal relationship to study protocol.

7.3.1 Causality

The terms used to assess the causal relationship of the event to the study drug are:

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- **Not Related:** There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

When the investigator assesses the AE as "not related", an alternative etiology (ie, concomitant drug, medical history, prior AE, or other etiologic reasons) must be provided.

The subject will be instructed to contact the Investigator immediately if he/she notices any unusual systemic or ocular AEs between visits.

Additional assessments/visits may be scheduled, as necessary, to ensure the safety of the subject, during the study period.

7.3.2 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself however may be of relatively minor medical significance (such as severe headache).

The terms used to assess the severity of the event are:

- **Mild:** Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate:** Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe:** Events interrupt the subject's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

7.3.3 Follow-Up

A subject who discontinues due to an AE should be seen for post-study follow-up visits as necessary.

When the severity and nature of the non-serious AEs (including non-related AEs of special interest, such as IOP increase, and non-serious AEs that are deemed not related to the study drug) that are ongoing at the study exit visit warrants a follow-up, the Investigator will do so as in the case of SAEs.

7.4 Reporting Serious Adverse Events and Follow-up

Any SAE must be reported to SynteractHCR Safety, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced from the date of consent through at least 30 days after the last dose of study drug must be reported to Synteract HCR regardless of the relationship to the study drug or the protocol. For events occurring beyond the minimum 30-day period after the last dose of study drug, or for any timeframe afterward deemed medically significant, only SAEs considered related to the study drug should be reported promptly to Synteract HCR Safety.

Within 24 hours of notification the Investigator will fax a completed Serious Adverse Event Report to the SynteractHCR contact noted on the Personnel and Facilities page. For SAEs with fatal outcomes, a summary of available autopsy findings should be submitted as soon as possible.

The Investigator will notify their IRB in writing of any SAE in accordance with the IRB requirements. For sites using a Central IRB (CIRB), Synteract HCR Clinical will notify the CIRB on their behalf.

Bausch + Lomb or its designee will be responsible for submitting SAE reports to regulatory authorities based on applicable regulations. Synteract HCR will be responsible to a notification to all participating Investigators of any SAE that is unexpected and associated with the study (refer to Section 7.6). If the Investigator becomes aware of any new information regarding an SAE (ie, resolution, change in condition, or new treatment), a new SAE Form must be completed and faxed to SynteractHCR Safety within 24 hours. The original SAE form is not to be altered. The report should be marked as a "follow-up report" and describe whether the event has resolved or continues and how the event was treated.

Serious adverse events that have previously been reported and that continue after the subject's discontinuation or completion of the study will be followed until their medical endpoints are determined or until no further change in the conditions is expected. The events and endpoints will be reported in writing by the Investigator to SynteractHCR Safety. Following the subject's discontinuation or completion of the study, for any timeframe afterward deemed medically significant, any SAEs that are assessed as causally related to study drug should also be reported to SynteractHCR Safety.

7.5 Reporting Pregnancies and Follow-up

In the event that a study subject or a study subject's partner becomes pregnant during the course of the study or within 7 calendar days after last dose of study drug, the study site will complete the Pregnancy Reporting form and will forward the completed form to the study Medical Monitor and the SynteractHCR Safety contact noted in the Personnel and Facilities page within 24 hours of the time the pregnancy was reported to the Investigator. The study site should also notify the IRB of the pregnancy, in accordance with IRB requirements. All pregnancies will be followed to term (in the event that a study subject's partner becomes pregnant, permission to follow the pregnancy needs to be granted by the partner). Every effort will be made to obtain the health status of the mother and infant or the fetus (including cases of miscarriage or therapeutic abortion). P regnancy outcome information must be documented on a follow-up Pregnancy Reporting form and submitted to the Medical Monitor, Synteract HCR and IRB.

The subject will be discontinued from the study to stop exposure of the study drug to the fetus.

7.6 Submitting an Expedited Safety Report to the IRB (Central or Local)

Any suspected, unexpected, serious adverse reaction (SUSAR) warrants expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or conduct of study), regardless if the study drug was administered, will be evaluated by Bausch + Lomb Global Safety and Vigilance to determine if expedited reporting is required. For example, an unexpected, serious and severe reaction which could be associated to the study procedures, and which could modify the study conduct requires expedited reporting.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A or Council for International Organizations of Medical Sciences I

Form, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study Medical Monitor. Once the report is compiled by Global Safety and Vigilance, the site Investigator must submit the expedited safety report to the local IRB/EC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The site principal Investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB. It is important that the principal Investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

8.0 STATISTICAL METHODS

8.1 Study Endpoints

8.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints for this study are:

1. The proportion of subjects with complete resolution of anterior chamber (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

8.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints for this study include:

- 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 AC cells and 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
- Proportion of treatment failures at Visit 5 (Postoperative Day 8)

Other secondary or exploratory efficacy analyses may also be carried out as described in the study Statistical Analysis Plan.

8.1.3 Safety Endpoints

The safety endpoints for this study are:

- Incidence of ocular and non-ocular AEs
- Change in IOP
- Ocular signs (biomicroscopy)
- Change in VA
- Change in dilated fundus exam

8.1.4 Tolerability Endpoints

The tolerability endpoints for this study are:

- Study drug sensation assessment at Visit 5 (Postoperative Day 8)
- Ocular symptoms at each follow-up visit

8.2 Hypotheses

The following multiple endpoints and multiple dose-vehicle comparison hypotheses will be tested using Bonferroni-based tree structured gatekeeping tests to control the overall type I error rate ($\alpha = 0.05$) for the primary efficacy endpoints over the entire study. [32, 33] The hypotheses in Family 1 will be tested simultaneously. Each hypothesis in Family 2 will be eligible for rejection only if the corresponding hypothesis (TID, BID) in Family 1 is rejected.

Family 1 of Hypotheses: Complete Resolution of AC Cells in the Study Eye at Visit 5

H_{011}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) = 0.

H_{A11}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed TID.

H_{012}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) = 0.

H_{A12}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with complete resolution of AC cells in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed BID.

Family 2 of Hypotheses: Complete Resolution of Pain in the Study Eye at Visit 5

H_{021}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) = 0.

H_{A21}: The difference, between subjects treated with LE gel 0.38% dosed TID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed TID.

H_{022}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) = 0.

H_{A22}: The difference, between subjects treated with LE gel 0.38% dosed BID and subjects treated with vehicle, in the proportion of subjects with Grade 0 pain in the study eye at Visit 5 (Postoperative Day 8) does not equal 0, with superiority claimed if the difference favors LE gel 0.38% dosed BID.

8.3 Sample Size

Approximately 588 subjects will be randomized in a 2:2:1:1 ratio to LE gel 0.38% dosed TID, LE gel 0.38% dosed BID, vehicle dosed TID, and vehicle dosed BID.

The 2 vehicle arms will be combined into 1 treatment group in the statistical analysis, and hence the study will have 3 treatment groups, ie, LE gel 0.38% dosed TID, LE gel 0.38% dosed BID, and (combined) vehicle group. Each of the three treatment groups will consist of approximately 196 subjects.

Estimates of efficacy used to calculate the sample size were based on the integrated database of 4 previous similar studies. Two of these studies were conducted with LE gel, 0.5% and vehicle, each dosed QID. One study was conducted with LE gel, 0.38%, dosed TID and BID. One study was conducted with LE gel, 0.38%, dosed BID.

Powers and sample sizes for individual comparisons were estimated using nQuery Advisor® 7.0 (Janet D. Elashoff, Copyright 1995-2007). Power to detect one or more differences and both differences was estimated by computer simulations of 250,000 trials.

8.3.1 Complete Resolution of AC cells in the Study Eye at Visit 5

A two group χ^2 test with a 0.025 two-sided significance level will have 87% power to detect the difference between a LE gel 0.38% proportion, π_1, of 0.283 and a vehicle proportion, π_2, of 0.143 (odds ratio of 0.423) when the sample size in each group is 196. The two simultaneous χ^2 tests (TID and BID) will have 95% power to detect at least one of two such differences and 80% power to detect both differences.

8.3.2 Complete Resolution of Pain in the Study Eye at Visit 5

Under the gatekeeping strategy, the power of each Family 2 (pain) hypothesis is limited by the power of the corresponding Family 1 (AC cells) hypothesis. However, the following statement shows that each Family 2 hypothesis is sufficiently powered in the event that the corresponding Family 1 hypothesis is rejected.

A two group χ^2 test with a 0.025 two-sided significance level will have 99% power to detect the difference between a LE gel 0.38% proportion, π_1, of 0.739 and a vehicle proportion, π_2, of 0.486 (odds ratio of 0.334) when the sample size in each group is 196.

8.4 Study Populations

Intent to Treat (ITT): The ITT population will include all randomized subjects. Analysis on the ITT sample will be used as the primary efficacy analysis and will be performed for all efficacy endpoints. Subjects will be analyzed in the treatment group to which they were assigned.

Per Protocol (PP): The PP population will include all ITT subjects who remain in study through Visit 5 (Postoperative Day 8) and who have not deviated from the protocol in any way likely to seriously affect the primary outcome of the study. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management, or subject assessment will be identified prior to locking the study database.

Analyses on the PP sample will be used as a supplement to the ITT analyses and will be performed for the primary efficacy endpoints. Subjects will be analyzed in the treatment group to which they were assigned.

Safety: The safety population will include all subjects who received at least 1 dose of study drug. All randomized subjects will be assumed to have taken study drug unless otherwise confirmed. If it is confirmed that a subject never took a dose of study drug, then the subject will be excluded from all safety analyses. All subjects in the safety population will be analyzed according to the treatment they actually received and not according to the treatment they were assigned to receive, in the event of discrepancy.

8.5 Statistical Analysis

8.5.1 Methods of Analysis

Summaries for continuous variables will include the sample size, mean, SD, median, minimum, and maximum. Minimums and maximums will be reported with the same precision as the raw values; medians and means will have 1 more decimal place; SD will have 2 more decimal places. Summaries for discrete variables will include the tabulation of frequencies and percentages. Differences between treatment groups will be calculated as LE gel 0.38% minus vehicle, and change from baseline will be calculated as follow-up visit minus baseline. The baseline visit will be defined as Visit 3 (Postoperative Day 1). For IOP, change from the previous visit will also be summarized.

8.5.1.1 Efficacy Endpoint Analyses

Analysis of Primary Efficacy Endpoints

The primary efficacy endpoints are the proportion of subjects with complete resolution of AC cells at Visit 5 (Postoperative Day 8) and the proportion of subjects with Grade 0 pain at Visit 5 (Postoperative Day 8). Primary efficacy analyses will be based on the intent-to-treat (ITT)

population with missing data imputed as failures (subjects placed on rescue medication prior to the visit being summarized will also be considered failures).

The primary efficacy analyses of the difference between each active treatment group and the combined vehicle treatment group at (Visit 5) Postoperative Day 8 will be tested using Pearson Chi-squared tests with p-values adjusted using a Bonferroni-based tree gatekeeping strategy with the structure shown in Table 3. [32, 33] Null hypotheses with adjusted p-values ≤ 0.05 will be rejected.

Table 3: Bonferroni-based tree gatekeeping hypothesis structure

Family	Null Hypothesis	Serial Rejection Set	Hypothesis Weight
F1	H_{11} (TID AC Cells Resolution)	NA	1/2
	H_{12} (BID AC Cells Resolution)	NA	1/2
F2	H_{21} (TID Pain Resolution)	$\{H_{11}\}$	1/2
	H_{22} (BID Pain Resolution)	$\{H_{12}\}$	1/2

95% confidence intervals will be constructed around the treatment differences using asymptotic normal approximations.

As a supportive analysis, these endpoints will be tested using the asymptotic Cochran Mantel-Haenszel statistic adjusting for site.

Supportive analyses of the primary analysis will be repeated on the per-protocol (PP) set.

Analysis of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be based on the ITT population. Missing data from subjects who are rescued or have discontinued the study prior to a study visit will be handled by either of two approaches: 1) missing data are imputed as failures; or 2) the last observation prior to the rescue medication or subject discontinuation is carried forward to subsequent visits (LOCF).

With the exception of change from baseline to each follow-up visit, each of the secondary efficacy endpoints will be independently tested at each visit using similar statistical methods employed for primary efficacy endpoints (without the p-value adjustments).

Change from baseline (Visit 3) in AC cells and flare composite score (Anterior Chamber Reaction), as well as individual cells and flare scores, will be analyzed using both continuous and discrete statistical methods by treatment and visit, with missing data imputed by LOCF.

Analysis of complete resolution of AC cells and Grade 0 pain at each visit will be conducted using a Pearson Chi-squared test, with missing data imputed as failures, and also with missing data imputed by LOCF. Similar analyses will be performed for complete resolution of AC cells and flare combined and for flare separately.

Other secondary or exploratory efficacy analyses may also be carried out as described in the study Statistical Analysis Plan.

8.5.1.2 Safety Endpoint Analyses

Safety endpoints will be summarized using discrete summary statistics by visit and treatment group.

Treatment-emergent AEs (TEAEs), defined as AEs that occur after the first dose of study medication, will be summarized prior to and after rescue medication and as ocular and non-ocular events separately. Ocular events will be summarized for treated eyes and fellow eyes separately. Non-treatment-emergent events will be presented only in the listings, with ocular and non-ocular events displayed separately.

A 95% confidence interval around the difference between treatment groups in the incidence of treatment-emergent AEs > 1% will be constructed using asymptotic normal approximations.

Biomicroscopy and Fundoscopy

Biomicroscopy findings will be summarized at each visit and at the worst case on treatment by subject and parameter, both prior to and after rescue medication use. Incidence of treatment-emergent events will be tested using both a Pearson Chi-squared test and a Cochran Mantel-Haenszel test

Fundoscopy measures will be summarized for screening and at Visit 6 (Postoperative Day 15) or upon study exit for early termination, for all subjects and subjects that had no rescue medication use. Incidence of treatment-emergent events will be tested using a Pearson Chi-squared test and a Cochran Mantel-Haenszel test adjusted for study sites.

Visual Acuity

Pinhole Snellen VA will be summarized at each visit as a categorical variable (20/20, 20/40, etc) and as a line change from baseline (Visit 3). Worst line change from baseline will also be presented. Visual acuity will be presented prior to and after rescue medication use. Subjects presenting a line change of > 2 lines will be tested using a Pearson Chi-squared test and a Cochran Mantel-Haenszel test adjusted for study sites.

IOP

Intraocular pressure will be summarized at each visit and by worst case on treatment for each subject using both continuous variable summaries (including change from baseline [Visit 3]) and discrete variable summaries. Results prior to and after rescue medication use will be presented separately. Discrete summaries will include:

- The proportion of subjects with change in IOP at any visit from screening (Visit 1) ≥ 5 mmHg and ≥ 10 mm Hg
- The proportion of subjects with change in IOP at any visit from baseline (Visit 3) ≥ 5 mmHg and ≥ 10 mm Hg
- The proportion of subjects with treatment-emergent IOP ≥ 30 mm Hg
- IOP at each visit categorized by IOP range: ≤ 5, 6 to 14, 15 to 21, 22 to 29, and ≥ 30 mmHg

- Change from screening in IOP at each visit categorized by IOP range: ≤ −5, −4 to 0,1 to 4, 5 to 9, 10 to 14, and ≥ 15 mm Hg
- Change from baseline (Visit 3) in IOP at each visit categorized by IOP range: ≤ −5, −4 to 0, 1 to 4, 5 to 9, 10 to 14, and ≥ 15 mm Hg

8.5.1.3 Tolerability Endpoint Analyses

Ocular Symptoms and Study Drug Sensation

Ocular symptoms will be summarized at each visit and presented by treatment separately for data obtained prior to receiving rescue medication and for data obtained after receiving rescue medication.

Study drug sensation data collected at Visit 5 (Postoperative Day 8) will be summarized by treatment group.

Tolerability endpoint analyses will use the Safety population with actual treatment received.

8.5.2 Subject Demographics and Baseline Characteristics

Race, gender, age, and iris color will be presented using discrete summary statistics by treatment group. Age will also be presented using continuous summary statistics by treatment group.

8.5.3 Medical and Ocular History

Medical history will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group. Ocular history will be summarized similarly for treated eyes and fellow eyes separately. If a subject reports the same preferred term multiple times within the same system organ class, then that preferred term will only be incremented by 1 within that system organ class, since subject counts will be presented. As with the preferred term, if a subject reports multiple conditions within the same system organ class, then that system organ class will only be incremented by 1, since subject counts will be presented.

8.5.4 Prior and Concomitant Medications

All medications will be coded using a World Health Organization drug dictionary. All non-study drugs (including prescribed and over-the-counter [OTC] medications) used within 30 days prior to study entry will be collected in the eCRF. All non-study drugs (including prescribed and OTC medications) used during the course of the study will be collected in the eCRF.

Concomitant medications will be summarized using categorical summary statistics in separate tables for non-ocular, ocular, and rescue therapy. Concomitant medications with partial dates will have their dates imputed. If the partial date is consistent with the first day of treatment, it will be imputed with this value. Otherwise, start dates will be imputed as the earliest possible date consistent with the partial data (first day of month/year) and end dates will be imputed as the latest possible date. If dates are entirely missing, the date will be imputed to the first day of treatment. Prior medications will be summarized in a listing.

8.5.5 Subject Disposition

Subject disposition will be summarized by treatment group using descriptive statistics for discrete variables. The categories will include all subjects who were randomized to each of the analysis populations (ITT, PP, and Safety), the number who completed the study and the number who discontinued the study (ITT and Safety) at any time along with the primary reason for early discontinuation. The primary reason for study discontinuation described in Section 6.2.3 will also be summarized and presented by treatment group.

8.5.6 Protocol Deviations

The number of subjects within each type of protocol deviation will be presented using discrete summary statistics. Protocol deviations will include, but are not limited to:

- Non-compliance with any scheduled study visit
- Non-compliance with study treatment
- Disallowed concomitant medications
- Non-compliance with study inclusion or exclusion criteria
- Non-compliance with study assessment procedures

Major protocol violations will be identified prior to the unmasking of study treatment during masked review of protocol deviations.

8.5.7 Treatment Compliance

Study drug compliance will be calculated for each subject by taking into account whether a subject takes all doses of study drug as instructed. Compliance will be based on the subject study diaries. The study drug compliance rate will be presented overall and by Visit 5 (Postoperative Day 8). The study drug compliance rate by Visit 5 (Postoperative Day 8) will be calculated as a percentage, with the total number of doses recorded in the study diary for the subject for the Visit 3-Visit 5 period divided by the total number of days times 2 (for those subjects dosing BID) or times 3 (for those subjects dosing TID) and then multiplying by 100.

As a secondary assessment of study drug use compliance, the overall study drug compliance rate will be calculated for a subject across the entire treatment period (ie, Visit 3-Visit 6). The overall compliance rate will be obtained by dividing the total number of doses recorded in the study diary by the total number of days times 2 (for those subjects dosing BID) or times 3 (for those subjects dosing TID) and then multiplying by 100. The day of Visit 6 (Postoperative Day 15) will not be included in the denominator, since subjects are not supposed to have a dose on that day (ie, any doses on that day would be over-compliance). The number and percentage of subjects in each of the following compliance rate categories will also be reported: $\leq 60\%$, 61 – 80%, 81 –100%, and $> 100\%$. Percentages will be calculated using the number of subjects who returned diaries from that dosing period as the calculation denominator. The number and percentage of subjects in each compliance rate category will be presented at Visit 5 (Postoperative Day 8) and overall.

8.5.8 Treatment Exposure

Extent of treatment exposure is defined as the total number of days from the first dose date to the last dose date, as recorded at the randomization study visit and the study exit eCRF page. Study treatment exposure will be calculated using subject study diary data. Duration of treatment exposure to study drug is calculated as:

Duration = date of last dose – date of first dose +1.

The extent of treatment exposure will be summarized in a table by summary statistics including the mean, SD, median, minimum, and maximum exposure. The summary will be further presented in the summary statistics table by treatment groups.

8.5.9 Missing Data

For the primary efficacy endpoints analyzed using the ITT analysis population, missing data for a subject and data from subjects discontinuing the study or treatment for any reason prior to Visit 5 will be imputed as treatment failures. These analyses will secondarily be presented using LOCF.

9.0 DATA QUALITY ASSURANCE

9.1 Study Monitoring

Bausch + Lomb representatives must be allowed to visit all study site locations to assess the data, quality of study performance, and study integrity in a manner consistent with applicable health authority regulations and the procedures described in this protocol by Bausch + Lomb.

Prior to the start of the study, Bausch + Lomb or its designee(s) will review the protocol, eCRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub/Co-Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, or per the study monitoring plan, during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements
- The integrity of the data is maintained, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remain qualified and able to conduct the study
- Study drug accountability is documented properly

During the course of the study, if Bausch + Lomb determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, Bausch + Lomb will take action to secure or reinstate compliance. In addition, Bausch + Lomb may terminate the

Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the remedial actions of Bausch + Lomb.

9.2 Source Documentation

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected and then entered onto the eCRF by site personnel. Source documentation consists of original subject documents as well as data and records with information relevant to the subject and his/her participation in the study.

Subject-completed forms such as diaries and questionnaires are also considered source data. Only subjects are to record information in subject diaries and questionnaires. In no instance, should an Investigator or study site personnel record any data or make changes to subject completed forms. The Unmasked designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (eg, an incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, dating, and writing subject's year of birth to acknowledge.

9.3 Case Report Forms and Data Verification

Subject data required by this protocol are to be recorded on eCRFs. The Investigator and study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc, and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. The eCRFs will be submitted to Bausch + Lomb or its designee(s) for quality assurance review, and statistical analysis.

A copy of the eCRFs will be retained by the Investigator at the conclusion of the study, who must ensure that it is stored in a secure place.

9.4 Recording of Data and Retention of Documents

Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and by their year of birth if also required. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator must retain essential documents indefinitely after the completion of the study, unless otherwise notified by Bausch + Lomb. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include but are not limited to the following:

- IRB approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB annual study review
- IRB correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- CRFs
- Subject's signed ICF
- FDA Form 1572
- Accountability records for the study drug
- Correspondence from and to Bausch + Lomb
- Any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (eg, retirement or relocation), study records will be transferred to a mutually agreed upon designee (eg, another Investigator or site IRB/EC). The Investigator will provide notice of such transfer in writing to Bausch + Lomb.

9.5 Auditing Procedures

Audits of clinical research activities in accordance with Bausch + Lomb's internal Standard Operating Procedures (SOPs) to evaluate compliance with the principles of GCP may take place. A regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority and/or IRB, the Investigator must inform Bausch + Lomb immediately that this request has been made.

9.6 Institutional Review Board/Ethics Committee Approval

The Investigator should ensure that participation in the study, in addition to the protocol, subject recruitment materials (written information or materials including web pages, radio advertisements, television spots or written text developed to encourage subject enrollment) and the ICF to be used in this study are approved by their institution IRB, or if not using their institution's IRB, approved by the reviewing central IRB prior to entering any subjects in the study. Documentation of IRB approval of the study protocol and informed consent must be provided to Bausch + Lomb prior to initiation of the study. In addition, the Investigator must ensure that the reviewing IRB has provided approval for any protocol amendments prior to implementation. If the amendment necessitates a revision to the ICF, the Investigator should ensure the revised form is also submitted to and approved by Bausch + Lomb and the IRB/EC prior to implementation.

9.7 Publication of Results

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by Bausch + Lomb or its designee and the Investigator(s) are completed. The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with Bausch + Lomb, and such that confidential or proprietary information is not disclosed.

Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to Bausch + Lomb or its designee for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Bausch + Lomb products and activities receive fair, accurate, and reasonable presentation.

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APPENDIX A: SCHEDULE OF VISITS AND PARAMETERS

All study tasks should be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator. All slit-lamp examinations, ophthalmoscopy, and IOP assessments conducted during the course of the study must be evaluated by an ophthalmologist.

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 authorization	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 (Goldman applanation tonometry) [d]	X		X	X	X	X	X	X
Dilated Fundus Exam	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

[a] All ophthalmic assessments will be performed bilaterally.
[b] Visit 2 must occur ≤ 14 days after the first screening assessment. Screening and surgery cannot take place on the same day.
[c] Visit 3 should occur 18 to 34 hours post-surgery. During this visit subject eligibility will be confirmed based on anterior chamber (AC) cell assessment.
[d] IOP should be assessed within ±2 hours of the time IOP was assessed at Visit 1 (Screening).
[e] Study drug dispensation and collection must be performed by the unmasked designee.
[f] Subjects should instill initial dose while in clinic. The investigator cannot be present for the in-office instillation.
[g] Collection of AEs extends from the time the subject gives informed consent until the last study visit.
[h] Dispense only.

[i] Check diary cards for accuracy and compliance. Must be performed by the unmasked designee
[j] Collect only.

APPENDIX B: METHODS OF CLINICAL EVALUATION

Any changes to the procedures described in this appendix will be provided under separate cover.

NOTE: Sites should use the same instrument and the same examiner when possible throughout the study. All ophthalmic assessments will be performed bilaterally.

1.0 OCULAR SYMPTOMS

The ocular symptoms of ocular pain, photophobia, itching, tearing, and ocular discharge are all to be graded by subjects using the following ordinal scales:

Ocular Pain: *A positive sensation of the eye, including foreign body sensation, stabbing, throbbing, or aching.*

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.
5 =	Severe:	Intense ocular, periocular or radiating pain (eg, constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics.

Photophobia:

0 =	Absent:	Absence of positive sensation.
1 =	Mild:	Very minimal light intolerance which may require some degree of sunglass protection to eliminate the symptom, noticed primarily in sunlight.
2 =	Moderate:	Infrequent or intermittent discomfort in the globe associated with exposure to room light or sunlight which is only partially relieved by dark glasses or subdued light. The symptoms still persist to some degree even with sunglasses.
3 =	Severe:	Constant or nearly constant pain in the eye that is not relieved by sunglasses and is only relieved by total occlusion of the eye. This total occlusion can be achieved with an eye patch or by closing the eyes. This sensation is so significant that frequently bed rest and occasionally systemic sedation is required to relieve this severe grade of symptom.

Itching:

0 =	Absent:	No desire to scratch or rub eyes.
1 =	Mild:	Occasional need to scratch or rub eyes but sensation is not completely absent.
2 =	Moderate:	Frequent need to scratch or rub eyes.
3 =	Severe:	Constant need to scratch or rub eyes.

Tearing:

0 =	Absent:	Normal tear production.
1 =	Mild:	Positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin.
2 =	Moderate:	Infrequent or intermittent spilling of tears over the lid margin.
3 =	Severe:	Constant or nearly constant spilling of tears over the lid margin; may be associated with blowing nose.

Ocular Discharge:

0 =	Absent:	No abnormal discharge.
1 =	Mild:	Small amount of mucopurulent or purulent discharge noted in the lower cul-de-sac. No true matting of eyelids upon awakening in the morning.
2 =	Moderate:	Moderate amount of mucopurulent or purulent discharge is noted in the lower cul-de-sac. Frank matting together of eyelids in the morning upon awakening.
3 =	Severe:	Profuse amount of mucopurulent or purulent discharge noted in the lower cul-de-sac and in the marginal tear strip. Eyelids tightly matted together upon awakening in the morning requiring warm soaks to pry lids apart.

2.0 STUDY DRUG SENSATION ASSESSMENT

Subject self-reported study drug sensation assessment at Visit 5 should describe the subject's overall or summary impression from Visit 3 through the day before Visit 5 for the degree of discomfort experienced immediately (ie, within 1 minute) after administering study drug. Study drug sensation will be graded on the following ordinal scale:

0 =	None:	No discomfort from the study drug.
1 =	Mild:	Mild discomfort from the study drug.

2 = Moderate: Moderate discomfort from the study drug.

3 = Severe: Severe discomfort from the study drug.

3.0 VISUAL ACUITY

Screening VA will be measured through a pinholed habitual unaided or historical correction using a S nellen chart. Study eye VA following cataract surgery will be measured unaided through a pinhole using a Snellen chart. The non-study eye VA will be measured at each visit through a pinholed habitual unaided or historical correction using a Snellen chart.

4.0 OCULAR SIGNS

A. BIOMICROSCOPY

A slit lamp examination of the anterior chamber, lids, conjunctiva, limbus, cornea, vitreous, and lens will be performed without pupil dilation. Cells and flare should be assessed using a high-power field slit beam of 1 mm x 1 mm. Ocular signs examined by slit lamp examination are to be graded using the following instructions and ordinal scales:

The methodology described below must be used by all investigators for evaluation and grading of anterior chamber ocular inflammation. A subject cannot be enrolled into the study if there is presence of any cells at the screening visit in either eye.

Anterior Chamber Cells Assessment Method

- Standardly used slit lamp biomicroscope, magnification, and beam strength
- Aim at central cornea in pupillary axis
- Focus on anterior aqueous humor
- At plane of focus, perform first count of cells (do not focus on multiple planes)
- Move focus to central cornea
- Refocus on anterior aqueous humor
- At plane of focus, perform second count of cells
- Convert each cell count to a grade (See anterior chamber cells grading scale below)
- Record both grades and the average of both grades on the source documentation

Cells: *Assess accumulation of white blood cells in anterior aqueous humor; pigmented cells and red blood cells are to be ignored.*

0 = No cells seen

1 = 1 – 5 cells

2 = 6 – 15 cells

3 = 16 – 30 cells

4 = >30 cells

Flare: *Assess scattering of a slit lamp light beam when directed into the anterior chamber (Tyndall effect).*

0 =	None:	No Tyndall effect.
1 =	Mild:	Tyndall effect barely discernible.
2 =	Moderate:	Tyndall effect in anterior chamber is moderately intense. Iris pattern is seen clearly.
3 =	Severe:	Tyndall effect in anterior chamber is severely intense. Iris pattern cannot be seen clearly.
4 =	Very Severe:	Tyndall effect is very severely intense. The aqueous has a white and milky appearance.

External Adnexa (Lids/Lashes): *Assess erythema or edema of the external adnexa. In addition to erythema or edema, any other abnormality of the lid and lashes that is observed will also be noted and graded according to the same 4-point grading scale.*

0 =	Absent	No erythema or edema
1 =	Mild	Erythema or edema present in only 1 segment of the lid or lash
2 =	Moderate	Diffuse erythema or edema present all over the lid or lash; edema does not protrude over the gray line
3 =	Severe	Erythema injection is marked or edematous swelling extends anterior to the gray line and outside of palpebral fissure

Ciliary Flush: *Assess external congestion of blood vessels surrounding the limbus.*

0 =	Absent
1 =	Present

Conjunctival Chemosis: *Assess swelling of the conjunctiva.*

0 =	Absent	No edema
1 =	Mild	Edema present in 1 segment of the bulbar conjunctiva
2 =	Moderate	Diffuse and uniform edema present all over the bulbar conjunctiva, edema does not protrude over the gray line
3 =	Severe	Conjunctival swelling extends anterior to the gray line, outside of palpebral fissure

Bulbar and Palpebral Conjunctival Injection: *Assess redness and swelling from dilated blood vessels in the bulbar and palpebral conjunctiva. It is at the Investigator's discretion whether the superior lid is inverted for assessing palpebral conjunctival injection; the same technique should be used for a given subject at each visit.*

0 =	Absent:	A normal, quiet eye; some subjects will exhibit rare vessels which are naturally prominent either by location or a large normal vessel diameter.
1 =	Mild:	Slightly dilated blood vessels; color of vessels is typically pink; can be quadrantic.
2 =	Moderate:	More apparent dilation of blood vessels; vessels color is more intense (redder); involves the vast majority of the vessel bed.
3 =	Severe:	Numerous and obvious dilated blood vessels; in the absence of chemosis the color is deep red – in the presence of chemosis, the leaking interstitial fluid may make the color appear less red or even pinkish; is not quadrantic.

Corneal Staining: *Assess after the instillation of fluorescein; fluorescein can be instilled either from a strip or as a 2% solution. A Wratten gel barrier filter will be provided by Bausch + Lomb for evaluation of corneal staining within 2-3 minutes after fluorescein instillation. The Wratten gel barrier filter must be used in the observation pathway when grading corneal staining, in combination with a cobalt blue exciter filter.*

0 =	None:	No fluorescein staining.
1 =	Trace:	Minimal superficial staining or stippling, and non-coalescing. Includes superficial foreign body staining.
2 =	Mild:	Lightly coalescent or diffuse punctate staining, with no stain diffusion into stroma.
3 =	Moderate:	Significant or densely coalescent punctate staining, including slight diffusion of stain into stroma.
4 =	Severe	Severe abrasion or erosion

Corneal Edema: *Assess degree of corneal edema.*

0 =	Absent	Clear cornea
1 =	Mild	Less than 25% of the cornea is clouded and thickened without Descemet's folds and with clear iris details
2 =	Moderate	25% – 50% of the cornea is clouded and thickened with few Descemet's folds and hazy iris details
3 =	Severe	More than 50% of the cornea is clouded and thickened with Descemet's folds and indistinguishable iris details

Lens Status: *Assess condition of the lens in the study eye*

At the screening visit only, lens status of the study eye will be noted as phakic, pseudophakic, or aphakic. If the lens is phakic, the absence or presence of nuclear sclerosis, cortical opacification, posterior subcapsular opacity, or pseudoexfoliation is to be noted.

Hyphema: *Assess presence or absence of hyphema.*

0 = Absent

1 = Present

Posterior Synechiae: *Assess for presence of adhesions between the iris and the lens.*

0 = Absent

1 = Present

Anterior Vitreous Haze: *Assess degree of vitreous haze by slit lamp examination of the anterior face of vitreous body.*

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

Precipitates: *Assess for presence of precipitates on implant and cornea.*

0 = Absent

1 = Present (If present, indicate the total number of precipitates)

Hypopyon: *Assess for presence of hypopyon.*

0 = Absent

1 = Present

B. DILATED FUNDUS EXAMINATION

A dilated fundus examination will be performed. The pupil will be dilated with an appropriate mydriatic drug. Mydriatic drugs should only be administered after all vision testing is complete. Ocular signs examined by dilated fundus examination are to be graded using the following instructions and ordinal scales:

Retina, Macula, and Choroid: *Assess for abnormalities in the retina, macula and choroid.*

0 = Normal

1 = Abnormal (If abnormal, indicate if clinically significant or not clinically significant)

Optic Nerve: *Assess for abnormalities in the optic nerve.*

0 = Normal

1 = Abnormal (If abnormal, indicate if clinically significant or not clinically significant)

Cup/Disc Ratio: *Assess the cup/disc ratio according to the following scale. Additionally, provide an estimate of the cup/disc ratio to at least one significant decimal place.*

0 = Normal

1 = Abnormal (If abnormal, indicate if clinically significant or not clinically significant)

5.0 INTRAOCULAR PRESSURE

Every attempt should be made to conduct the IOP measurement at approximately the same time of day for every visit.

Intraocular pressure will be preferably measured using a Goldmann applanation tonometer. Study sites should calibrate the Goldmann applanation tonometer according to the manufacturer's instructions. The IOP assessment should be carried out before pupillary dilation. The IOP in both eyes will be measured, with the right eye preceding the left eye.

For a Goldmann applanation tonometer, the operator should initially set the dial to 10 mmHg, then look through the slit lamp and adjust the dial to take the reading, and then record the results.

- The procedure will be repeated on the same eye twice consecutively.
- If the measurements are within 2 mmHg or less of each other, the mean of the 2 readings will be recorded as the IOP at that time point.
- If the 2 readings are more than 2 mmHg different from each other, a third (consecutive) reading will be taken and the median (middle) IOP value will be recorded as the IOP at that time point.

Preferably, the same operator should measure IOP and the same tonometer should be used at each visit for a given subject.