SPONSOR APPROVAL PAGE

Bausch & Lomb Incorporated

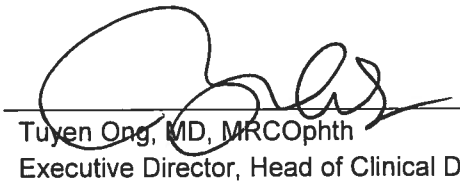
A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract

Protocol Administrative Change Memo 1, 19 Aug 2013

Study 670 Protocol, Amendment 6, 22 May 2013

Attached is a Protocol administrative change memo for Study 670, Amendment 6, dated 22 May 2013, approved by the signatories below.

Approved By:



19th August 2013

Tuyen Ong, MD, MRCOphth
Executive Director, Head of Clinical Development
Global Pharmaceuticals
Bausch & Lomb Incorporated

Date

Mary Harrell, BsBM, RAC (US)
Senior Manager, Regulatory Affairs
Global Pharmaceuticals
Bausch & Lomb Incorporated

Date

Ken Harper, BS
Director, Clinical Programs
Global Pharmaceuticals
Bausch & Lomb Incorporated

Date

Xiaohui Luo, PhD
Director, Biostatistics
Global Pharmaceuticals
Bausch & Lomb Incorporated

Date

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Bausch & Lomb Incorporated

A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract

Protocol Administrative Change Memo 1, 19 Aug 2013

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Tuyen Ong, MD, MRCOphth
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Date

Mary Harrell, BsBM, RAC (US)
Senior Manager, Regulatory Affairs
Global Pharmaceuticals
Bausch & Lomb Incorporated

8/19/2013
Date

Ken Harper, BS
Director, Clinical Programs
Global Pharmaceuticals
Bausch & Lomb Incorporated

19 Aug 2013
Date

Xiaohui Luo, PhD
Director, Biostatistics
Global Pharmaceuticals
Bausch & Lomb Incorporated

19 Aug 2013
Date

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BAUSCH + LOMB

TO: Protocol Distribution Log Listing for Bausch & Lomb Study 670 Protocol, Amendment 6, dated 22 May 2013

FROM: Michael Zhang, Study Manager, Pharmaceuticals

RE: Study # 670 Protocol, Amendment 6, dated, 22 May 2013, Administrative Changes, dated 19 Aug 2013

The purpose of this letter is to inform you of minor clarifications or administrative changes to Bausch & Lomb Study 670, entitled "*A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract".* These clarifications are administrative in nature. They do not meet the criteria for a protocol amendment as they have no impact on clinical decision-making procedures, a subject's health, safety, or welfare, or study design.

Page	Section	Description of Change or Clarification	Rationale
4	Personnel and Facilities	Change Scientific & Clinical Affairs/Medical Monitor from: "James Gow, MD Clinical Affairs Bausch & Lomb Incorporated 50 Technology Drive Irvine, CA 92618-2301 US Tel: + 1 949 788 5359 Mobile: + 1 949 701 6398 Email: james.gow@bausch.com" To: "Jon I. Williams, PhD Director, Clinical Affairs Bausch & Lomb Incorporated 50 Technology Drive Irvine, CA 92618 US Tel: + 1 949 788 5334 Mobile: + 1 949 345 5703 Email: Jon.Williams@bausch.com"	Administrative change.

16 38	Synopsis – Hypothesis 7.2	Change from: "…where μ_{LE} and μ_{PR} are the mean grade of anterior chamber inflammation at Visit **4** (Postoperative Day **7**) for LE Ophthalmic Gel, 0.5%..." To: "…where μ_{LE} and μ_{PR} are the mean grade of anterior chamber inflammation at Visit **5** (Postoperative Day **14**) for LE Ophthalmic Gel, 0.5%..."	Typographical error remaining from previous amendment.

Note: The Statistical Analysis Plan (SAP) will be am ended prior to database lock to correct this error. Additionally, country-specific translations of the Study 670 s ynopsis and/or protocol may reflect correction of this error in the translated document.

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SUMMARY OF CHANGES

STUDY #670

A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract

AMENDMENT 6, 22 MAY 2013

Deletions indicated by ~~strikethrough~~; additions indicated by **bold**.

Section	Page	Description of Change or Clarification	Rationale
As applicable	As applicable	Update to revision chronology and footers.	Administrative change.
As applicable	As applicable	Corrected grammatical and punctuation errors.	Clarification.
As applicable	As applicable	Changed Visit 6 from Postoperative Day ~~29~~ to Day **28**.	Changed per FDA Written Request.
Sponsor Approval Page	2	Updated Biostatistics Sponsor Signatory as follows: "~~Tesfaye Liranso, PhD~~ ~~Principal Biostatistician~~ **Xiaohui Luo, PhD** **Director, Biostatistics**"	Administrative change.
Investigator Statement of Approval	3	Changed instructions on page as follows: "Upon signing, provide ~~a copy~~ **the original** of this page to Bausch + Lomb and retain a copy for your files."	Clarification.
Personnel and Facilities page	4-5	Updated study personnel information as follows: "~~Laura Trusso, MS~~ **Michael Zhang** **Study Manager** Bausch & Lomb Incorporated ~~1400 North Goodman Street~~ ~~Rochester, NY 14609~~ **7 Giralda Farms, Suite 1001** **Madison, NJ 07940** **US** Tel: +1 ~~585 338 5561~~ **973 360 6448** Mobile: +1 ~~585 747 4187~~ **973 610 3294** Fax: +1 ~~585 338 0788~~ **585 338 0606** Email: ~~Laura_Trusso@bausch.com~~ **Michael.Zhang@bausch.com** **AP Sites:** **Paul Park** **Clinical Study Manager** **Bausch & Lomb (S) Pte Ltd**	Administrative change.

Section	Page	Description of Change or Clarification	Rationale
		151 Lorong Chuan #04-03A **New Tech Park, Lobby C** **Singapore 556741** **Tel: +65 6490 5858** **Mobile: + 65 9230 3963** **Fax: +65 6286 4218** **Email: Paul.Park@bausch.com** ~~Sharon W. Adams~~ ~~Executive Director, Global Head of Pharmacovigilance~~ **Saberi Rana Ali, MBBS, MS (Ophth), MPH** **Associate Director, Global Safety and Vigilance** Bausch & Lomb Incorporated ~~8500 Hidden River Parkway~~ **7 Giralda Farms, Suite 1001** ~~Tampa, FL 33637~~ **Madison, NJ 07940** Tel: +1 ~~813 866 2585~~ **973 360 6478** Fax: +1 813 975 7750 Mobile: +1 ~~813 240 5853~~ **862 579 8366** **SAE Inbox: SAE@bausch.com** **<u>AP Sites:</u>** **Global Safety and Vigilance, Asia Pacific** **Bausch & Lomb Korea** **13F, KT&G Kosmo Daechi-Tower,** **#945-10 Daechi-dong, Gangnam-gu,** **Seoul 135-280, Korea** **Tel: + 82 70 7167 9784** **Mobile: + 82 10 9112 9784** **Fax: + 82 2 6442 1460** **Email: safety.asia@bausch.com** ~~Raphaele Siou-Mermet, MD, MS~~ ~~Manager, European Pharmaceutical Clinical Science~~ ~~Laboratoire Chauvin/Bausch & Lomb~~ ~~416 Rue Samuel Morse, CS 99535~~ ~~34961 Montpellier Cedex 2~~ ~~France~~ **James Gow, MD** **Clinical Affairs** **Bausch & Lomb Incorporated** **50 Technology Drive** **Irvine, CA 92618-2301** **US** Tel: + ~~33 1 60 87 14 91~~ **1 949 788 5359** ~~Fax: + 33 1 60 87 14 75~~ Mobile: +~~33 6 19 53 06 90~~ **1 949 701 6398** Email: ~~Raphaele.Siou-Mermet@bausch.com~~ **james.gow@bausch.com** **<u>AP Sites:</u>** **Zuellig Pharma Korea Clinical Trial** **2nd Floor 213-7** **Jangji-Ri, Dongtan-Myun** **Hwasung-City** **Gyunggi-Do**	

Section	Page	Description of Change or Clarification	Rationale
		445-812 **Korea**"	
List of Abbreviations	8	Added the following entries: AP | Asia Pacific Bausch + Lomb | Bausch & Lomb Incorporated	Clarification.
Synopsis	8	Changed number of subjects and regions as follows: "Approximately ~~158~~ **140** subjects at approximately 30 investigative sites in the United States (US)**,** ~~and~~ European Union (EU)**, and Asia Pacific (AP)** will be enrolled in this study."	Updated sample size to align with statistical recommendations from FDA Written Request and administrative change to regions.
Synopsis	9	Changed description of the phase of the study as follows: "Phase ~~3b~~ **4**"	Updated to align with the FDA Written Request that the study be conducted as a Phase 4 post-marketing commitment study to satisfy pediatric evaluation requriements.
Synopsis 3.1 (Study Design) 3.4 (Study Duration)	9 18 22	Changed description of study duration as follows: "Study duration will be approximately ~~12-18~~ **11-19** weeks…"	Updated to align with visit window changes in FDA Written Request.
Synopsis 3.1 (Description of Study Design Including Choice of Control Groups)	9 18	Changed number of subjects and regions as follows: "Approximately ~~158~~ **140** subjects will be enrolled in this double-masked, parallel-group, active-controlled study at approximately 30 investigative sites in the United States (US)**,** ~~and~~ European Union (EU)**, and Asia Pacific (AP)**. A total of ~~158~~ **140** subjects aged 0-11 years will be randomized in a 1:1 ratio to LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1%. Of the ~~158~~ **140** randomized subjects, at least ~~79~~ **60** subjects (approximately ~~40~~ **30** subjects per treatment group) will be in the age range from 0-3 years. Prednisolone Acetate Ophthalmic Suspension, 1% was chosen as the active-control because it has a long history as the standard of care in the US."	Updated sample size to align with statistical recommendations from FDA Written Request and administrative change to regions.
Synopsis 3.1 (Description of Study Design Including Choice of Control Groups)	9 18-19	Changed window of Visit 1 and Visit 6 as follows: "… Subjects will visit the clinic eight times. Visit 1 will be the Screening Visit and will occur up to a maximum of ~~6 weeks~~ **29 days** prior to surgery."	Changed per FDA Written Request.
Synopsis 3.2.1.2 (Exclusion Criteria)	11 21	Changed exclusion criterion #11 as follows: "Female subjects who have started menarche prior to Visit 1 (Screening) ~~or during the study~~."	Clarification.

Section	Page	Description of Change or Clarification	Rationale
Synopsis 5.1.1 (Visit 1)	11-12 26-27	Changed visit window and text for Visit 1 as follows: "Visit 1 (Screening, ~~≤ 42 Days Prior to Surgery~~ **Day -15 ±14 days**) … • obtain assent (when applicable), written informed consent (US**,** ~~and~~ EU**, and AP**) and HIPAA authorization (US only) … NOTE: Surgery will be scheduled to occur within ~~6 weeks~~ **29 days** of the Screening Visit. **Screening and surgery cannot take place on the same day.**"	Changed per FDA Written Request, clarification, and administrative change.
Synopsis 5.1.2 (Visit 2)	12 27	Changed visit window for Visit 2 as follows: "Visit 2 (Surgery/Randomization, ~~≤ 42 Days of Screening~~ **Day 0 [within 29 days of screening]**)"	Changed per FDA Written Request.
Synopsis 5.1.4 (Visit 4)	13 27	Changed visit window for Visit 4 as follows: "Visit 4 (Postoperative Day 7, ±~~1~~**2** day**s**)"	Changed per FDA Written Request.
Synopsis 5.1.5 (Visit 5)	14 29	Changed visit window for Visit 5 as follows: "Visit 5 (Postoperative Day 14, ±~~1~~**3** day**s**)"	Changed per FDA Written Request.
Synopsis 5.1.6 (Visit 6)	14 29	Changed visit window for Visit 6 as follows: "Visit 6 (Postoperative Day 2~~9~~**8**, ±~~3~~**7** days; End of Treatment)"	Changed per FDA Written Request.
Synopsis 5.1.7 (Visit 7)	14 30	Changed visit window for Visit 7 as follows: "Visit 7 (Postoperative Day 42, ±~~3~~**7** days)"	Changed per FDA Written Request.
Synopsis 5.1.8 (Visit 8)	15 30	Changed visit window for Visit 8 as follows: "Visit 8 (Postoperative Day 90, ±~~3~~**14** days; Study Exit)"	Changed per FDA Written Request.
Synopsis 7.1.1 (Primary Efficacy Endpoints)	15 37	Changed primary efficacy endpoint from Visit 4 to Visit 5, as follows: "…mean grade of anterior chamber inflammation at ~~Visit 4 (Postoperative Day 7)~~ **Visit 5 (Postoperative Day 14)**"	Changed per FDA Written Request.
Synopsis 7.1.2 (Secondary Efficacy Endpoints)	15 37	Changed secondary efficacy endpoint from Visit 5 to Visit 4, as follows: "mean grade of anterior chamber inflammation at Visits ~~5~~ **4** and 6 (Postoperative Days ~~14~~**7** and 2~~9~~**8**)"	Changed to align with primary endpoint changes.
Synopsis 7.3 (Sample Size)	16 38	Updated sample size calculation as follows: "~~A sample size of 124 subjects (62 subjects per treatment group) yields 80% power to detect non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% using a non-inferiority upper limit of 0.50. This sample size assumes a common standard deviation of 0.98 and an expected difference of 0 for the difference in means between treatment groups using anterior chamber inflammation at Visit 4 (Postoperative Day 7). The standard deviation is obtained by pooling the standard deviations of the LE and vehicle arms from the integrated adult studies of LE Gel in post cataract surgery[8,9]. The absolute upper limit of the 95% CI for the treatment effect from the pooled data was 0.57. From a clinical~~	1) Changed power calculation to be based on ITT population per FDA Draft Guidance for Industry, Non-Inferiority Clinical Trials (March 2010). 2) Assumption (standard deviation and non-inferiority margin) aligned with FDA Written Request.

Section	Page	Description of Change or Clarification	Rationale
		~~perspective and based on this upper limit of 0.57, a non-inferiority margin of 0.50 is selected. The 0.50 unit is < 0.57 and represents clinically one half of the smallest increment on the grading scale of anterior chamber inflammation. These sample size calculations utilize a one-sided, level alpha = 0.025 non-inferiority analysis. Of the 124 subjects randomized, at least 62 subjects will be in the age group 0-3 years. As the percentage of subjects with rescue medication was 8% at Day 8 in one adult study (highest value), it is estimated that in children, 12% can require rescue medication. Assuming a subject dropout rate of 12% for rescue medication, it is necessary to enroll 141 subjects. Furthermore, assuming a 10% rate for major protocol violations, 158 subjects (79 per treatment group) will be randomized to obtain 124 PP subjects at the completion of the study.~~ **A sample size of 120 subjects (60 subjects per treatment group) yields 98% power to detect non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1%. This sample size assumes a common standard deviation of 0.47, a two-sided alpha=0.05, a non-inferiority margin of 0.35 and an expected difference of 0 for the difference in means between treatment groups using anterior chamber inflammation at Visit 5 (Postoperative Day 14). Assuming a subject dropout rate (including the initiation of rescue medication) of 12%, approximately 140 subjects will be randomized of which at least 60 subjects will be in the age group 0-3 years as per the FDA's Written Request.**"	
Synopsis 7.2 (Hypothesis)	16 38	Changed non-inferiority margin as follows: "H_o: $\mu_{LE} - \mu_{PR} \geq$ ~~0.50~~ **0.35** versus H_a: $\mu_{LE} - \mu_{PR} <$ ~~0.50~~ **0.35**"	Changed per FDA Written Request.
Synopsis	16	Changed primary efficacy endpoint listed in Primary Analysis as follows: "For the primary efficacy analysis, the mean grade of anterior chamber inflammation at Visit ~~4~~ **5** (Postoperative Day ~~7~~ **14**) will be calculated by treatment group, including a two-sided 95% CI about the difference between the means. If the upper limit of the 95% CI is less than ~~0.50~~ **0.35**, then non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% will be claimed."	Changed per FDA Written Request.
Synopsis	16	Changed description of Primary Analysis as follows: "The primary efficacy analysis will be based on the ~~Per Protocol (PP) set~~ **ITT population**. The primary analysis will be repeated ~~for the ITT set~~ **using the PP population** to supplement the ~~PP~~ **ITT** analysis. Any discrepancy between the 2 analyses will be explained."	Changed to follow FDA Draft Guidance for Industry, Non-Inferiority Clinical Trials (March 2010).

Section	Page	Description of Change or Clarification	Rationale
Synopsis	16	Changed endpoints listed in Secondary Efficacy Analysis as follows: "The secondary efficacy analyses will ~~include~~ **be conducted based on** ~~all subjects in~~ the ITT **population as well as** ~~and~~ **the** PP ~~sets~~ **population**. As a secondary analysis, the analysis of the mean grade of anterior chamber inflammation will be repeated as above for Visits ~~5~~**4** and 6 (Postoperative Days ~~1~~**4**7 and 2~~9~~**8**, respectively)."	Clarification and changed to align with change in primary endpoint.
Synopsis 7.6.1 (Methods of Analysis)	17 40	Added text to MedDRA dictionary description as follows: "All AEs will be coded using a MedDRA dictionary **(the most current version available at the start of the study will be used)**."	Clarification.
3.2 (Selection of Study Population)	19	Updated number of subjects as follows: "Approximately ~~158~~ **140** subjects who have undergone routine, uncomplicated surgery for childhood cataract will be enrolled in this clinical investigation."	Changed to align with sample size changes.
3.2.4 (Subject Discontinuation	21	Added the "**onset of menarche during the study**" as a reason that a subject must be discontinued prior to the final study visit.	Added for subject safety based on the update to exclusion criterion #11.
3.3 (Investigators)	22	Updated study regions as follows: "The study will be conducted at approximately 30 investigative sites located in the US**,** ~~and~~ EU**, and AP**."	Administrative change.
3.4 (Study Duration)	22	Updated description of study duration as follows: "Visit 1 will be the Screening Visit and will occur up to a maximum of ~~42~~ **29** days prior to surgery."	Changed per FDA Written Request.
3.5 (Treatments)	22	Changed treatment description as follows: "A total of ~~79~~ **140** subjects will be ~~randomized~~ **randomly assigned in a 1:1 ratio** to receive **either** LE Ophthalmic Gel, 0.5%~~ and 79 subjects will be randomized to receive~~ **or** Prednisolone Acetate Ophthalmic Suspension, 1%."	Clarification and changed to align with sample size changes.
4.5 (Packaging and Labeling)	24	Added Asia Pacific information as follows: "The medication will be identified as a new drug, limited by federal law**,** ~~and~~ EU Directive**, and AP local regulation** to investigational use**,** and appropriately labeled for investigational use for this age group."	Administrative change.
4.10 (Selection of Dose)	26	Updated description of Lotemax as follows: "This regimen was selected for the study based on the dose regimen of the currently marketed Lotemax (LE Ophthalmic ~~Suspension~~ **Gel**, 0.5%) and is also the treatment recommended in the Package Insert (PI) and Summary of Product Characteristics (SmPC) of the comparator drug."	Administrative change.

Section	Page	Description of Change or Clarification	Rationale
6.4 (Reporting SAEs and Follow-up)	35-36	Added Asia Pacific information as follows: "For US sites, these should be reported to Bausch + Lomb Global Safety & Vigilance; for EU sites, these should be reported to the EU Study Manager who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance**; for AP sites, these should be reported to Bausch + Lomb AP Global Safety & Vigilance (Seoul, Korea), who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance (Madison, NJ, US)**. … For US sites, the events and endpoints will be reported in writing by the Investigator to Bausch + Lomb Global Safety & Vigilance**;** ~~**or,**~~ for the EU sites, the SAE form should be sent to the EU Study Manager who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance**;** ~~**,**~~ **for AP sites, these should be reported to Bausch + Lomb AP Global Safety & Vigilance (Seoul, Korea), who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance (Madison, NJ, US).** … should also be reported to **Bausch + Lomb** Global Safety & Vigilance."	Administrative change and clarification.

Section	Page	Description of Change or Clarification	Rationale
6.4 (Reporting SAEs and Follow-up)	35-36	Updated SAE contact information as follows: "US Sites: ~~Sharon W. Adams~~ ~~Executive Director, Global Head of Pharmacovigilance~~ ~~Bausch & Lomb Incorporated~~ ~~8500 Hidden River Parkway~~ ~~**Tampa, Florida 33637**~~ **Saberi Rana Ali, MBBS, MS (Ophth), MPH** **Associate Director, Global Safety and Vigilance** **Bausch & Lomb Incorporated** **7 Giralda Farms, Suite 1001** **Madison, NJ 07940** US ~~Tel: +1 813 866 2585~~ ~~Fax: +1 813 975 7750~~ ~~Mobile: +1 813 240 5853~~ **Tel: +1 973 360 6478** **Fax: +1 813 975 7750** **Mobile: +1 862 579 8366** **SAE Inbox: SAE@bausch.com** **AP Sites:** **Bausch + Lomb Asia Pacific Global Safety and Vigilance** **Bausch & Lomb Korea** **13F, KT&G Kosmo Daechi-Tower,** **#945-10 Daechi-dong, Gangnam-gu,** **Seoul 135-280, Korea** **Tel: + 82 70 7167 9784** **Mobile: + 82 10 9112 9784** **Fax: + 82 2 6442 1460** **Email: safety.asia@bausch.com**"	Administrative change.
6.6 (Medical Monitor)	37	Updated Medical Monitor information as follows: "~~Raphaele Siou-Mermet, MD, MS~~ ~~Manager, European Pharmaceutical Clinical Science~~ ~~Laboratoire Chauvin/Bausch & Lomb~~ ~~416 Rue Samuel Morse, CS 99535~~ ~~34961 Montpellier Cedex 2~~ ~~France~~ **James Gow, MD** **Clinical Affairs** **Bausch & Lomb Incorporated** **50 Technology Drive** **Irvine, CA 92618-2301** **US** Tel: +~~33 1 60 87 14 91~~**1 949 788 5359** ~~Fax: + 33 1 60 87 14 75~~ Mobile: +~~33 6 19 53 06 90~~**1 949 701 6398** ~~Email: Raphaele.Siou-Mermet@bausch.com~~ **james.gow@bausch.com**"	Administrative change.

Section	Page	Description of Change or Clarification	Rationale
7.4 (Randomization)	39	Updated the sample size as follows: "A total of ~~158~~ **140** subjects from ages 0-11 will be randomized to receive LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1% in a 1:1 ratio. The subgroup age 0-3 years will **consist of at least 60 subjects** ~~be randomized in approximately equal proportion~~."	Changed to align with sample size changes.
7.5 Analysis Sets	39	Updated section as follows: "7.5 Analysis ~~Sets~~ **Populations** The analysis ~~sets~~ **populations** that will be used in this study are: • Intent-to-Treat (ITT) ~~Set~~ **Population**: includes all subjects who were randomized and have at least one post-treatment assessment. Analysis on the ITT ~~set~~ **population** will be used for ~~secondary~~ **primary** efficacy analyses and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized. ~~Analysis on the primary endpoint on the ITT set will be used to supplement the Per Protocol analysis.~~ • Per Protocol (PP) ~~Set~~ **Population**: includes all of the subjects in the ITT ~~set~~ **population** that remained in the study through ~~Visit 4~~ **Visit 5** (Postoperative Day ~~7~~ **14**) and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study. ~~Analyses on the PP set will be used for the primary efficacy analysis and will be performed for the primary and secondary efficacy endpoints,~~ **Analysis using the PP population will be used to supplement the ITT analysis,** analyzing subjects according to the treatment received."	Clarification and changed to align with FDA Draft Guidance for Industry, Non-Inferiority Clinical Trials (March 2010).

Section	Page	Description of Change or Clarification	Rationale
7.6.1 Methods of Analysis	39-40	Updated the description of primary efficacy analysis as follows: "The primary efficacy analysis will be based on the ~~Per Protocol (PP) set~~ **ITT population with missing data imputed using the last observation carried forward (LOCF) method** and the primary endpoint mean grade of anterior chamber inflammation at ~~Visit 4~~ **Visit 5** (Postoperative Day ~~7~~ **14**). The mean grade of anterior chamber inflammation at ~~Visit 4~~ **Visit 5** (Postoperative Day ~~7~~ **14**) will be analyzed using an analysis of variance (ANOVA) model with treatment as a classification variable. …The null hypothesis will be rejected and non-inferiority established if the upper limit of the confidence interval does not exceed ~~0.50~~ **0.35**. **To supplement the primary analyses, the analyses above will be repeated for the PP population; no imputation will be conducted for missing data. Any discrepancy between the ITT and PP analyses will be explained.** ~~The last observation carried forward (LOCF) imputation method implements the idea that a subject's anterior chamber inflammation is unchanged after dropout, an assumption that needs to be checked for plausibility. To this end, a sensitivity analysis of the primary endpoint using the ITT set will be performed.~~ The secondary efficacy analyses will **be conducted based on** ~~include all subjects in~~ the ITT **population as well as** ~~and~~ **the** PP ~~sets~~ **population**. As a secondary analysis, the analysis of the mean grade of anterior chamber inflammation will be repeated as above for Visits ~~5~~**4** and 6 (Postoperative Days ~~1~~**47** and 2~~9~~**8**, respectively)."	Changed to align with FDA Written Request, changed to follow FDA Draft Guidance for Industry, Non-Inferiority Clinical Trials (March 2010), and clarification.
7.6.3 Subject Disposition	40-41	Updated descriptions of study populations as follows: "• subjects randomized (ITT ~~set~~ **population**) • subjects treated (Safety ~~set~~ **population**) • subjects in the PP ~~set~~ **population**"	Clarification.
7.6.7 Missing Data	41	Updated missing data description as follows: "~~Subjects with missing data or with rescue medication prior to Day 7 will be excluded from the primary PP analysis.~~ For the primary efficacy endpoint analyzed using the ITT ~~set~~ **population**, missing data and data from subjects placed on rescue medication will be ~~analyzed~~ **imputed** using the LOCF methodology. ~~For the secondary efficacy endpoints analyzed using the ITT set, missing data and data from subjects placed on rescue medication prior to the visit being summarized will be imputed as LOCF and will also be summarized as missing.~~ **For the PP analysis, missing data and data from subjects placed on rescue medication will not be imputed.**"	Clarification and changed to align with change in primary efficacy endpoint.

Section	Page	Description of Change or Clarification	Rationale
8.2 Source Documentation	42	Added Asia Pacific information as follows: "…If an entry is found to be illegible or a mistake is found (eg, incorrect year was recorded), the subject's parent/legal guardian should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, and dating and initialing (US **and AP** only)/writing year of birth to acknowledge (EU only) the change."	Administrative change.
8.6 IRB/EC Approval	43	Added Asia Pacific information as follows: "In the US **and AP**, the Investigator, or in the EU… … In addition, in the US **and AP**, the Investigator, or in the EU…"	Administrative change.
9.0 References	45	Deleted the following references: "~~[10] National Research Council (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academic Press.~~ ~~[11] Ratitch, B., O'Kelly, M., Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures, PharmaSUG2011 - Paper SP04.~~ ~~[12] SAS Institute Inc. 2008. SAS/STAT ® 9.2 User's Guide. Cary, NC: SAS Institute Inc.~~"	Administrative change.
Appendix A	A-1	Updated the following items in the Schedule of Visits and Parameters: "Visit 1 Screening ~~-6 Weeks~~ **Day -15 (±14 days)** Visit 4 Follow-up Day 7 (±~~1~~**2** day**s**) Visit 5 Follow-up Day 14 (±~~1~~**3** day**s**) Visit 6 Follow-up/End Treatment Day 2~~9~~**8** (±~~3~~**7** days) Visit 7 Follow-up Day 42 (±~~3~~**7** days) Visit 8 Study Exit Day 90 (±~~3~~**14** days) [2] Visit 2 must occur within ~~6 weeks~~ **29 days** of Visit 1. [5] Fundoscopy will be performed bilaterally either at Visit 2 (surgery/randomization) or Visit 3 (postoperative day 1), at Visit 5 (postoperative day 14 ±~~1~~**3** day**s**), and at Visit 8 (postoperative day 90 ±~~3~~**14** days)."	Changed per FDA Written Request.

TITLE PAGE

A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract

PROTOCOL

IND #102654 and EudraCT#2010-024388-41

STUDY #670

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.

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Amendment 5		04 Jun 2012
Amendment 6		22 May 2013

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SPONSOR APPROVAL PAGE

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The final document associated with this signature approval is maintained in the ClinOps Documentum system.

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INVESTIGATOR STATEMENT OF APPROVAL

A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract

PROTOCOL

IND #102654 and EudraCT#2010-024388-41

STUDY #670

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, and 312, 42 USC 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 of this page to Bausch + Lomb and retain a copy for your files.

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

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LIST OF ABBREVIATIONS

Abbreviation/Acronym	Term
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ANOVA	Analysis of Variance
AP	Asia Pacific
BAK	Benzalkonium Chloride
Bausch + Lomb	Bausch & Lomb Incorporated
BID	Twice a Day
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CFR	Code of Federal Regulations
dpt	Diopter
eCRF	Electronic Case Report Form
EC	Ethics Committee
EU	European Union
FDA	United States Food and Drug Administration
GCPs	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IOL	Intraocular Lens
IOP	Intraocular Pressure
ITT	Intent-to-Treat
LDPE	Low Density Polyethylene
LE	Loteprednol Etabonate
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not At Random
NSAID	Nonsteroidal Anti-inflammatory Drug
PI	Package Insert
PMM	Pattern Mixture Model
PP	Per Protocol
QD	Once a Day
QID	Four Times a Day
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
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 Study #670	
Title:	**A Randomized, Multicenter, Double Masked, Parallel-Group Study Assessing the Safety and Efficacy of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Prednisolone Acetate Ophthalmic Suspension, 1% for the Treatment of Intraocular Inflammation Following Surgery for Childhood Cataract**
Phase of study:	Phase 4
Number of study centers and subjects:	Approximately 140 subjects at approximately 30 investigative sites in the United States (US), European Union (EU), and Asia Pacific (AP) will be enrolled in this study.
Planned study period:	Study duration will be approximately 11-19 weeks depending on the time between screening, the day of surgery, and the last study visit (Visit 8, Postoperative Day 90). The enrollment period is expected to be completed in 24 months.
Objective(s):	The primary objective is to compare the efficacy and safety of Loteprednol Etabonate (LE) Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% for the treatment of postoperative inflammation following ocular surgery for childhood cataract.
Study design:	Approximately 140 subjects will be enrolled in this double-masked, parallel-group, active-controlled study at approximately 30 investigative sites in the United States (US), European Union (EU), and Asia Pacific (AP). A total of 140 subjects aged 0-11 years will be randomized in a 1:1 ratio to LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1%. Of the 140 randomized subjects, at least 60 subjects (approximately 30 subjects per treatment group) will be in the age range from 0-3 years. Prednisolone Acetate Ophthalmic Suspension, 1% was chosen as the active-control because it has a long history as the standard of care in the US. Study duration will be approximately 11-19 weeks from screening to the last visit (Visit 8, Postoperative Day 90). Subjects will visit the clinic eight times. Visit 1 will be the Screening Visit and will occur up to a maximum of 29 days prior to surgery. Visit 2 will be on the day of surgery. At the end of surgery on Visit 2, eligibility for randomization into the study will be assessed and, if appropriate, subjects will be randomized at this time. Randomized subjects will complete postoperative study Visits 3 through 8 (Postoperative Days 1, 7, 14, 28, 42, and 90, respectively). Subject's eyes meeting eligibility criteria at both Visit 1 (Screening) and Visit 2 (Surgery/Randomization) will be randomized to receive study medication. If both eyes of a subject undergo routine, uncomplicated surgery at Visit 2 (Surgery/Randomization) and meet eligibility criteria, the subject's right eye will be considered the study eye. In the event that the subject requires surgery on the contralateral eye at any time during the study, the fellow eye will be treated with standard of care medication. The subject will receive the first dose of study drug by the unmasked designee at the end of the surgery. Either the unmasked designee or the subject's parent/legal guardian will then administer 1 to 2 drops of study drug to the lower cul-de-sac of the study eye once in the evening on the day of surgery and then four times a day (QID), at approximately four hour intervals, beginning on the morning after surgery. QID dosing will continue until postoperative day 14, including dosing at appropriate time intervals on the day of a visit. Treatment will be tapered from QID to twice a day (BID) during the interval between postoperative days 15 and 21. Treatment will be further tapered from postoperative day 22 until day 28 to once a day (QD) with the last dose being

	administered on the day prior to Visit 6 (Postoperative Day 28).
Criteria for inclusion:	This study will include subjects who meet the following criteria at Visit 1 (Screening): 1. Subjects who are male or female, 0 to 11 years of age, on the date the Informed Consent Form (ICF) is signed. 2. Subjects who have the ability to understand and provide assent (when applicable) and whose parent/legally authorized representative has the ability to understand and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF and provide authorization as appropriate for local privacy regulations. 3. Subjects whose parent/legally authorized representative is able and willing to comply with all treatment and follow-up procedures. 4. Subject is a candidate for routine, uncomplicated surgery for childhood cataract (aspiration, with or without posterior capsulotomy with or without anterior vitrectomy, and with or without posterior chamber intraocular lens (IOL) implantation, not combined with any other surgery and without the planned use of iris hooks and/or pupil stretching). This study will include subjects who meet the following criteria at Visit 2 (Surgery/Randomization): 1. Subjects who have undergone routine, uncomplicated surgery for childhood cataract (aspiration, with or without posterior capsulotomy, with or without anterior vitrectomy, and with or without posterior chamber IOL implantation, not combined with any other surgery).
Criteria for exclusion:	This study will exclude subjects who meet the following criteria: 1. Subjects who have a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment or follow-up, eg: – presence of any active or suspected viral, bacterial, or fungal disease in the study eye – subjects with post-traumatic cataract in the study eye – active uveitis in the study eye – ocular neoplasm in the study eye 2. Subjects with glaucoma, ocular hypertension, or those receiving intraocular pressure (IOP) lowering therapy in either eye or systemically. 3. Subjects with a history of steroid-induced IOP elevation in either eye. 4. Subjects who have suspected permanent low vision or blindness (eg, legal definition of blindness: visual acuity [VA] of ≤ 20/200 or visual field of ≤ 20 degrees) in the fellow non-study eye. (The study eye must not be the subject's only sighted eye.) 5. Subjects who have had ocular surgery (including laser therapy) in the study eye within 90 days prior to randomization on Visit 2 (Surgery/Randomization). 6. Subjects who are expected to require treatment with systemic or ocular (study eye) corticosteroids other than study drug during the 90 days following cataract surgery or have used any systemic or ocular corticosteroids (study eye) within 14 days prior to cataract surgery. (Ocular therapy with corticosteroids in the fellow eye is permitted.) 7. Subjects who are expected to require concurrent systemic or ocular therapy (study eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), or concurrent ocular therapy (either eye) with mast cell stabilizers, antihistamines, or decongestants during the 90 days following cataract surgery or have received any of the above medications within 2 days prior to surgery (intraoperative NSAIDs for mydriasis in the study eye are NOT

	permitted; ocular therapy with NSAIDs in the fellow eye is permitted). 8. Subjects who are expected to require concurrent ocular (either eye, eg, Restasis) or systemic immunosuppressant therapy during the 90 days following cataract surgery or have used ocular (either eye) immunosuppressants within 30 da ys prior to surgery or systemic immunosuppressants within 10 months prior to surgery. 9. Subject or subject's breastfeeding mother or wet nurse who is expected to use corticosteroids (except corticosteroid inhalers and dermatological corticosteroids, as long as they are not used on the eyelids or surrounding area) or immunosuppressants during the 90 days following cataract surgery. 10. Subjects who have a history or presence of chronic generalized systemic disease that the Investigator believes may either increase the risk to the subject or confound the results of the study (eg, Diabetes mellitus, human immunodeficiency virus [HIV], acquired immunodeficiency syndrome [AIDS]). 11. Female subjects who have started menarche prior to Visit 1 (Screening). 12. Subjects who have known hypersensitivity or other contraindication to the study drug(s) or any components in the drug formulation. 13. Subjects who have participated in an investigational drug or device study within 30 days prior to Visit 1 (Screening). 14. Subjects who were previously randomized in this study.
Investigational product:	Loteprednol Etabonate Ophthalmic Gel, 0.5%, contains the active ingredient loteprednol etabonate 0.5% and the preservative benzalkonium chloride (BAK), 0.003%. It also contains the inactive ingredients glycerin, propylene glycol, sodium chloride, polycarbophil, sodium hydroxide, tyloxapol, edetate disodium dihydrate, boric acid, and water for injection.
Comparator product(s):	Prednisolone Acetate Ophthalmic Suspension, 1% contains the active ingredient prednisolone acetate 1% and the preservative BAK 0.004%. The inactive ingredients are comprised of: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate. The pH during its shelf life ranges from 5.0 - 6.0.
Duration of treatment:	The subject will receive the first dose of study drug by the unmasked designee at the end of the surgery. Either the unmasked designee or the subject's parent/legal guardian will then administer 1 to 2 dr ops of study drug to the lower cul-de-sac of the study eye once in the evening on the day of surgery and then QID, at approximately four hour intervals, beginning on the morning after surgery. QID dosing will continue until postoperative day 14, including dosing at appropriate time intervals on the day of a visit. Treatment will be tapered from QID to BID during the interval between postoperative days 15 a nd 21. Treatment will be further tapered from postoperative day 22 until day 28 to QD with the last dose being administered on the day prior to Visit 6 (Postoperative Day 28). ***NOTE: At the conclusion of surgery, each randomized subject will receive the first dose of study drug from the unmasked designee followed by an antibiotic of the Investigator's choice and an eye patch.***
Study procedures:	**Visit 1 (Screening, Day -15 ±14 days)** Visit 1 will proceed as follows: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • obtain assent (when applicable), written informed consent (US, EU, and AP) and HIPAA authorization (US only) • determine if the subject meets preliminary eligibility criteria: – documentation of demographic information

	– current and relevant medical and ophthalmic history – concomitant medications • if the subject meets the preliminary eligibility criteria, the following assessments will be performed: – ocular symptoms – pediatric visual acuity (VA) testing – biomicroscopy – IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy*** ***NOTE: Surgery will be scheduled to occur within 29 days of the Screening Visit. Screening and surgery cannot take place on the same day.*** **Visit 2 (Surgery/Randomization, Day 0 [within 29 days of Screening])** Visit 2 will proceed as follows: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • record adverse events (AEs) and changes in concomitant medications • pediatric VA assessment • biomicroscopy • IOP measurement • fundoscopy, if performed during surgery, if not, then perform at Visit 3 • immediately following surgery, determine eligibility ***NOTE: Subjects who, in the Investigator's opinion, have surgical complications such that it is not in their best interest to continue in the study are considered screen failures and will not be randomized into the trial.*** ***If during the surgery it is determined that additional manipulations, such as pupil stretching or the use of iris hooks are required, it is left to the Investigator's discretion whether or not it is safe to randomize the subject into the trial.*** ***At the conclusion of the surgery, no subconjunctival or intracameral steroid injections are permitted. If a steroid injection is deemed necessary by the Investigator, the subject cannot be randomized and is considered a screen failure.*** • randomize eligible subjects by assigning the next sequential subject kit box • the unmasked designee must weigh both bottles of study drug prior to dispensing • at the conclusion of surgery, the randomized subject will receive the first dose of study drug from the unmasked designee followed by an antibiotic of the Investigator's choice and an eye patch • study drug will be dispensed to the subject's parent/legal guardian by the unmasked designee • a study drug administration diary will be provided to the subject's parent/legal guardian who will be instructed to record the time of each instillation and to bring the diary and study drug (both bottles) to each visit. The subject's parent/legal guardian will be reminded that no other information should be recorded in the diary • the subject's parent/legal guardian will be trained by site personnel with regard to the correct instillation of eye drops prior to administration of the initial dose at any time at Visit 1 or 2 without using the study drug, but prior to their first instillation of study drug outside of the office. The time and method is left to the Investigator's discretion

	• either the unmasked designee or the subject's parent/legal guardian will administer approximately one to two drops of study drug into the lower cul-de-sac of the study eye in the evening, after removing the patch and before applying the shield, which will cover the study eye overnight • the subject's parent/legal guardian will proceed with administration of the study drug on the morning of the first postoperative day with QID dosing at approximately four hour intervals, independently of when Visit 3 is scheduled to occur **Visit 3 (Postoperative Day 1; First Calendar Day after Surgery)** At Visit 3, the following assessments will be performed: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • AEs and changes in concomitant medications • the unmasked designee must weigh both bottles of study drug • ocular symptoms • pediatric VA • biomicroscopy • IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy.*** ***NOTE: If, at any time point after surgery, IOP is elevated, treatment or intervention is left to the Investigator's discretion and the subject is to continue the study.*** • fundoscopy, if not performed during surgery ***NOTE: Topical antibiotic drops should be administered at least 15 minutes AFTER study drug application.*** • review and collect study drug administration diary for compliance. Instruct subject's parent/legal guardian to record time of each instillation on the diary and to bring the diary and study drug (both bottles) to their next visit. Remind subjects that no other information should be recorded in the diary • dispense new diary • the unmasked designee must redispense study drug • instruct subject's parent/legal guardian to continue dosing the study drug QID, at approximately four hour intervals for the next 2 weeks **Visit 4 (Postoperative Day 7, ±2 days)** At Visit 4, the following assessments will be performed: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • AEs and changes in concomitant medications • the unmasked designee must weigh both bottles of study drug • ocular symptoms • pediatric VA • biomicroscopy • IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy*** • review study drug administration diary for compliance. Instruct subject's parent/legal guardian to record time of each instillation in the diary and to bring the diary and study drug (both bottles) to their next visit. Remind

	subject's parent/legal guardian that no other information should be recorded in the diary • dispense new diary • the unmasked designee must redispense study drug • remind subject's parent/legal guardian that the dosing is QID for another week and then BID for one week **Visit 5 (Postoperative Day 14, ±3 days)** At Visit 5, the following assessments will be performed: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • AEs and changes in concomitant medications • the unmasked designee must weigh both bottles of study drug • ocular symptoms • pediatric VA • biomicroscopy • IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy*** • fundoscopy (it is at the Investigator's discretion whether to perform fundoscopy with or without mydriasis) • review study drug administration diary for compliance. Instruct subject's parent/legal guardian to record time of each instillation in the diary and to bring the diary and study drug (both bottles) to their next visit. Remind subject's parent/legal guardian that no other information should be recorded in the diary • dispense new diary • the unmasked designee must redispense study drug • remind subject's parent/legal guardian that the dosing is BID for the rest of the week and QD for the last week **Visit 6 (Postoperative Day 28, ±7 days; End of Treatment)** At Visit 6, the following assessments will be performed: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • AEs and changes in concomitant medications • the unmasked designee must weigh both bottles of study drug and collect all used and unused study drug (both bottles) • collect diaries • ocular symptoms • pediatric VA • biomicroscopy • IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy*** **Visit 7 (Postoperative Day 42, ±7 days)** At Visit 7, the following assessments will be performed: ***NOTE: All ocular assessments and VA will be performed bilaterally.***

	• AEs and changes in concomitant medications • ocular symptoms • pediatric VA • biomicroscopy • IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy*** **Visit 8 (Postoperative Day 90, ±14 days; Study Exit)** At Visit 8, the following assessments will be performed: ***NOTE: All ocular assessments and VA will be performed bilaterally.*** • AEs and changes in concomitant medications • ocular symptoms • pediatric VA • biomicroscopy • IOP measurement ***NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy*** • fundoscopy (it is at the Investigator's discretion whether to perform fundoscopy with or without mydriasis) • subject exits from study
Study endpoints:	**Primary Efficacy Endpoints** • mean grade of anterior chamber inflammation at Visit 5 (Postoperative Day 14). **Secondary Efficacy Endpoints** • mean grade of anterior chamber inflammation at Visits 4 and 6 (Postoperative Days 7 and 28) • proportion of subjects with Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 anterior chamber inflammation at each visit (Postoperative Days 7, 14, and 28) • presence/absence and total area, if present, of synechiae at each visit (Postoperative Days 7, 14, and 28) • presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28) **Safety Endpoints** • incidence of overall and specific AEs • type and incidence of AEs at each visit • change in IOP from baseline (Visit 2, Surgery/Randomization) to each visit • greatest IOP change from baseline - including the measurement at Visit 3 (Postoperative Day 1) • greatest IOP change from baseline - excluding the measurement at Visit 3 (Postoperative Day 1) • ocular signs (biomicroscopic examination of the lids, conjunctiva, cornea, anterior chamber without pupil dilation) at each visit **Tolerability Endpoint** • ocular symptoms at each visit
Statistical methods:	Summaries for continuous variables will include the sample size, mean,

standard deviation (SD), median, minimum, and maximum. Summaries for discrete variables will include the tabulation of frequencies and percentages. Means and medians will be presented to one more decimal place than the recorded data. Standard deviations will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Confidence intervals (CIs) will be presented using the same number of decimal places as the parameters (eg, mean). Percentages will be presented to one decimal place.

Sample Size

A sample size of 120 subjects (60 subjects per treatment group) yields 98% power to detect non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1%. This sample size assumes a common standard deviation of 0.47, a two-sided alpha=0.05, a non-inferiority margin of 0.35 and an expected difference of 0 for the difference in means between treatment groups using anterior chamber inflammation at Visit 5 (Postoperative Day 14). Assuming a subject dropout rate (including the initiation of rescue medication) of 12%, approximately 140 subjects will be randomized of which at least 60 subjects will be in the age group 0-3 years as per the FDA's Written Request.

Hypothesis

Test for the non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% will be primarily based on the following one-sided null hypothesis (H_o) and alternative hypothesis (H_a):

$$H_o: \mu_{LE} - \mu_{PR} \geq 0.35 \quad \text{versus} \quad H_a: \mu_{LE} - \mu_{PR} < 0.35$$

where μ_{LE} and μ_{PR} are the mean grade of anterior chamber inflammation at Visit 4 (Postoperative Day 7) for LE Ophthalmic Gel, 0.5% and Prednisolone Acetate Ophthalmic Suspension, 1% treatment group, respectively.

Primary Analysis

For the primary efficacy analysis, the mean grade of anterior chamber inflammation at Visit 5 (Postoperative Day 14) will be calculated by treatment group, including a two-sided 95% CI about the difference between the means. If the upper limit of the 95% CI is less than 0.35, then non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% will be claimed.

The primary efficacy analysis will be based on the ITT population. The primary analysis will be repeated using the PP population to supplement the ITT analysis. Any discrepancy between the 2 analyses will be explained.

Secondary Efficacy Analysis

The secondary efficacy analyses will be conducted based on the ITT population as well as the PP population.

As a secondary analysis, the analysis of the mean grade of anterior chamber inflammation will be repeated as above for Visits 4 and 6 (Postoperative Days 7 and 28, respectively).

Additional secondary analyses include:

- the proportion of subjects with anterior chamber inflammation with Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 for each visit (Postoperative Days 7, 14, and 28)
- the proportion of subjects with presence/absence and total area, if present, of synechiae for each visit (Postoperative Days 7, 14, and 28)

	• the proportion of subjects with presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28) For each of the above endpoints, treatment groups will be compared using the Pearson Chi-squared test or fisher's exact test as appropriate. Differences between the proportions of treatment groups and 95% confidence interval about the differences will be presented. Subgroup analyses will be performed for anterior chamber inflammation, anterior chamber cells, and anterior chamber flare as appropriate by method of assessment (slit lamp versus penlight with handheld magnifying 20 diopter lens), country (region), age group, IOL implantation, and iris color. **Safety Analysis** All subjects in the safety set will be included in the safety analyses. Intraocular pressure will be summarized by visit using continuous summaries (including change from baseline and change from screening) for the following items: • change in IOP from baseline to each visit • greatest IOP change from baseline - including the one day postoperative measurement at Day 1 • greatest IOP change from baseline - excluding the one day postoperative measurement at Day 1 • ocular signs (biomicroscopic examination of the lids, conjunctiva, cornea, anterior chamber without pupil dilation) Treatment emergent systemic AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group. Treatment emergent ocular AEs will be summarized for treated eyes and fellow eyes separately. Similarly, treatment emergent AEs will be summarized by severity and relationship separately. All AEs will be coded using a Med DRA dictionary (the most current version available at the start of the study will be used). **Tolerability** Ocular symptoms will be summarized using discrete summary statistics by visit and treatment group. These data will be summarized under the safety analyses.

1.0 INTRODUCTION

Corticosteroids are potent, non-specific, anti-inflammatory drugs that inhibit a variety of chemotactic substances and factors that mediate capillary permeability, contraction of nonvascular smooth muscle, and vasodilation. In addition, corticosteroids suppress inflammation by inhibiting edema, fibrin deposition, migration of leukocytes, and phagocytic activity.

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 eye.[1] Although corticosteroids are widely used as a topical agent for ocular inflammation, most possess a safety risk profile that limits their general utility. A common risk associated with corticosteroid therapy is an elevation of intraocular pressure (IOP).[2,3] In addition, chronic use of topical corticosteroids may result in the development of cataracts.[4]

Loteprednol etabonate (LE) is a novel compound designed as a unique C-20 ester corticosteroid[5] that will undergo a predictable transformation to an inactive metabolite. The relatively rapid metabolism of LE to an inactive metabolite improves the safety profile of this corticosteroid. In clinical studies, LE Ophthalmic Suspension, 0.5% (Lotemax®) has been shown to have a decreased incidence of clinically significant IOP increase (ie, ≥10 mm Hg) compared to prednisolone acetate.[6,7] This characteristic of LE makes it an optimal candidate for use in inflammatory ocular conditions.

The pH of LE Ophthalmic Gel, 0.5% was adjusted to 6.0 - 6.5 making it closer to normal physiological pH of 7.4. Preservative effectiveness has been demonstrated in this new formulation using a reduced level of the preservative, benzalkonium chloride (BAK), than in the currently marketed product (ie, from 100ppm or 0.01% to 30 ppm or 0.003%), which may improve the tolerability of the gel.

2.0 OBJECTIVE

The primary objective is to compare the efficacy and safety of Loteprednol Etabonate (LE) Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% for the treatment of postoperative inflammation following ocular surgery for childhood cataract.

3.0 STUDY DESIGN

3.1 Description of Study Design Including Choice of Control Groups

Approximately 140 subjects will be enrolled in this double-masked, parallel-group, active-controlled study at approximately 30 investigative sites in the United States (US), European Union (EU), and Asia Pacific (AP).

A total of 140 subjects aged 0-11 years will be randomized in a 1:1 ratio to LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1%. Of the 140 randomized subjects, at least 60 subjects (approximately 30 subjects per treatment group) will be in the age range from 0-3 years. Prednisolone Acetate Ophthalmic Suspension, 1% was chosen as the active-control because it has a long history as the standard of care in the US.

Study duration will be approximately 11-19 weeks from screening to the last visit (Visit 8, Postoperative Day 90). Subjects will visit the clinic eight times. Visit 1 will be the

Screening Visit and will occur up to a maximum of 29 days prior to surgery. Visit 2 will be on the day of surgery. At the end of surgery on Visit 2, eligibility for randomization into the study will be assessed and, if appropriate, subjects will be randomized at this time. Randomized subjects will complete postoperative study Visits 3 through 8 (Postoperative Days 1, 7, 14, 28, 42, and 90, respectively).

Subject's eyes meeting eligibility criteria at both Visit 1 (Screening) and Visit 2 (Surgery/Randomization) will be randomized to receive study medication. If both eyes of a subject undergo routine, uncomplicated surgery at Visit 2 (Surgery/Randomization) and meet eligibility criteria, the subject's right eye will be considered the study eye. In the event that the subject requires surgery on the contralateral eye at any time during the study, the fellow eye will be treated at the Investigator's discretion with standard of care medication.

The subject will receive the first dose of study drug by the unmasked designee at the end of the surgery. Either the unmasked designee or the subject's parent/legal guardian will then administer 1 to 2 drops of study drug to the lower cul-de-sac of the study eye once in the evening on the day of surgery and then four times a day (QID), at approximately four hour intervals, beginning on the morning after surgery. QID dosing will continue until postoperative day 14, including dosing at appropriate time intervals on the day of a visit. Treatment will be tapered from QID to twice a day (BID) during the interval between postoperative days 15 and 21. Treatment will be further tapered from postoperative day 22 until day 28 to once a day (QD) with the last dose being administered on the day prior to Visit 6 (Postoperative Day 28).

3.2 Selection of Study Population

Approximately 140 subjects who have undergone routine, uncomplicated surgery for childhood cataract will be enrolled in this clinical investigation.

3.2.1 Eligibility

3.2.1.1 Inclusion Criteria

This study will include subjects who meet the following criteria at Visit 1 (Screening):

1. Subjects who are male or female, 0 to 11 years of age, on the date the Informed Consent Form (ICF) is signed.
2. Subjects who have the ability to understand and provide assent (when applicable) and whose parent/legally authorized representative has the ability to understand and provide written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved ICF and provide authorization as appropriate for local privacy regulations.
3. Subjects whose parent/legally authorized representative is able and willing to comply with all treatment and follow-up procedures.
4. Subject is a candidate for routine, uncomplicated surgery for childhood cataract (aspiration, with or without posterior capsulotomy with or without anterior vitrectomy, and with or without posterior chamber intraocular lens (IOL) implantation, not combined with any other surgery and without the planned use of iris hooks and/or pupil stretching).

This study will include subjects who meet the following criteria at Visit 2 (Surgery/Randomization):

1. Subjects who have undergone routine, uncomplicated surgery for childhood cataract (aspiration, with or without posterior capsulotomy, with or without anterior vitrectomy, and with or without posterior chamber IOL implantation, not combined with any other surgery).

3.2.1.2 Exclusion Criteria

This study will exclude subjects who meet the following criteria:

1. Subjects who have a severe/serious ocular condition, or any other unstable medical condition that, in the Investigator's opinion, may preclude study treatment or follow-up, eg:
   - presence of any active or suspected viral, bacterial, or fungal disease in the study eye
   - subjects with post-traumatic cataract in the study eye
   - active uveitis in the study eye
   - ocular neoplasm in the study eye
2. Subjects with glaucoma, ocular hypertension, or those receiving intraocular pressure (IOP) lowering therapy in either eye or systemically.
3. Subjects with a history of steroid-induced IOP elevation in either eye.
4. Subjects who have suspected permanent low vision or blindness (eg, legal definition of blindness: visual acuity [VA] of $\leq$ 20/200 or visual field of $\leq$ 20 degrees) in the fellow non-study eye. (The study eye must not be the subject's only sighted eye.)
5. Subjects who have had ocular surgery (including laser therapy) in the study eye within 90 days prior to randomization on Visit 2 (Surgery/Randomization).
6. Subjects who are expected to require treatment with systemic or ocular (study eye) corticosteroids other than study drug during the 90 days following cataract surgery or have used any systemic or ocular corticosteroids (study eye) within 14 days prior to cataract surgery. (Ocular therapy with corticosteroids in the fellow eye is permitted.)
7. Subjects who are expected to require concurrent systemic or ocular therapy (study eye) with nonsteroidal anti-inflammatory drugs (NSAIDs), or concurrent ocular therapy (either eye) with mast cell stabilizers, antihistamines, or decongestants during the 90 days following cataract surgery or have received any of the above medications within 2 days prior to surgery (intraoperative NSAIDs for mydriasis in the study eye are NOT permitted; ocular therapy with NSAIDs in the fellow eye is permitted).
8. Subjects who are expected to require concurrent ocular (either eye, eg, Restasis) or systemic immunosuppressant therapy during the 90 days following cataract surgery or have used ocular (either eye) immunosuppressants within 30 days prior to surgery or systemic immunosuppressants within 10 months prior to surgery.
9. Subject or subject's breastfeeding mother or wet nurse who is expected to use corticosteroids (except corticosteroid inhalers and dermatological corticosteroids, as

long as they are not used on the eyelids or surrounding area) or immunosuppressants during the 90 days following cataract surgery.

10. Subjects who have a history or presence of chronic generalized systemic disease that the Investigator believes may either increase the risk to the subject or confound the results of the study (eg, Diabetes mellitus, human immunodeficiency virus [HIV], acquired immunodeficiency syndrome [AIDS]).
11. Female subjects who have started menarche prior to Visit 1 (Screening).
12. Subjects who have known hypersensitivity or other contraindication to the study drug(s) or any components in the drug formulation.
13. Subjects who have participated in an investigational drug or device study within 30 days prior to Visit 1 (Screening).
14. Subjects who were previously randomized in this study.

3.2.2 Subject Completion

The subject has completed the study when Visit 8 (Postoperative Day 90) has been completed and the subject has been exited. Subjects who require further follow-up for an AE will be followed according to Section 6.3 and 6.4.

3.2.3 Rescue Therapy

Subjects will be assessed at Visits 3 through 6 (Postoperative Days 1, 7, 14, and 28) for rescue. A study eye with greater than anticipated inflammation at Visit 3 or, at the following visits, a worsening or no change of the grade of inflammation compared to the previous visit may be eligible for rescue therapy. In some cases a persistent or worsening inflammation may be due to a lack of compliance. This should be explored and rectified. If the Investigator deems rescue necessary, the choice of rescue therapy and dosing shall be determined by the Investigator. Subjects requiring rescue therapy for inflammation will stop treatment with study medication. The subject should be exited from the study and the reason selected for exit should be “rescue therapy” in the eCRF. This should not be reported as an AE unless determined to be an SAE.

3.2.4 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’s parent/legally authorized representative not following required study procedures

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

- voluntary withdrawal
- onset of menarche during the study
- death

- Investigator decision that it is not in the best medical interest of the subject to continue participation in the investigation
- requires rescue medication

Prior to discontinuing a subject, every effort should be made to contact the subject's parent/legal guardian, schedule a final study visit, and obtain as much follow-up data as possible, and to retrieve all study materials. Adverse events will be followed as described in Section 6.3 and 6.4. Subject withdrawals will be documented clearly on the source document and applicable electronic case report form (eCRF). The assessments scheduled for Visit 8 (Postoperative Day 90) should be performed at this early termination visit.

Subject discontinuation will be documented clearly on the applicable eCRF. Any subject discontinued from the study after randomization will not be replaced.

3.2.5 Lost to Follow-up

Subjects who do not return for scheduled follow-up Visits 3 through 8, as defined by the visit window and cannot be contacted via two telephone calls and one letter with delivery confirmation are 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.

3.3 Investigators

The study will be conducted at approximately 30 investigative sites located in the US, EU, and AP.

The 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 all applicable regulatory requirements. Sub-Investigators will be identified on the FDA Form 1572 and in the regulatory documents required by the country in which the study is being conducted.

Each Investigator will enroll approximately 5 subjects. In the event that selected sites do not meet full enrollment, the Sponsor may decide to increase enrollment as needed at other currently active sites and additional site(s) may be added to satisfy the enrollment requirements of the study.

3.4 Study Duration

Study duration will be approximately 11-19 weeks depending on the time between screening, the day of surgery, and the last study visit (Visit 8, Postoperative Day 90). The enrollment period is expected to be completed in 24 months.

Eligible subjects who are enrolled in the study will be seen for eight scheduled study visits. Visit 1 will be the Screening Visit and will occur up to a maximum of 29 days prior to surgery. Visit 2 will be on the day of surgery. At the end of surgery on Visit 2, eligibility for randomization into the study will be assessed and, if appropriate, subjects will be randomized at this time. Randomized subjects will complete postoperative study Visits 3 through 8 (Postoperative Days 1, 7, 14, 28, 42, and 90, respectively).

3.5 Treatments

A total of 140 subjects will be randomly assigned in a 1:1 ratio to receive either LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1%.

4.0 STUDY MATERIALS

4.1 Description of Test Article

Loteprednol Etabonate Ophthalmic Gel, 0.5%, contains the active ingredient loteprednol etabonate 0.5% and the preservative benzalkonium chloride (BAK), 0.003%. It also contains the inactive ingredients glycerin, propylene glycol, sodium chloride, polycarbophil, sodium hydroxide, tyloxapol, edetate disodium dihydrate, boric acid, and water for injection.

4.2 Description of Comparator

Prednisolone Acetate Ophthalmic Suspension, 1% contains the active ingredient prednisolone acetate 1% and the preservative BAK 0.004%. The inactive ingredients are comprised of: boric acid; edetate disodium; hypromellose; polysorbate 80; purified water; sodium bisulfite; sodium chloride; and sodium citrate. The pH during its shelf life ranges from 5.0 - 6.0.

4.3 Instructions for Use and Administration

Following the initial drop administration by the unmasked study personnel at the end of the surgery, either the unmasked designee or the subject's parent/legal guardian will administer 1 to 2 drops of study drug into the study eye once in the evening on the day of surgery and then QID, at approximately four hour intervals, beginning on the morning after surgery. QID dosing will continue until postoperative day 14. Treatment will be tapered from QID to BID during the interval between postoperative days 15 and 21. Treatment will be further tapered from postoperative day 22 until day 28 to QD with the last dose being administered on the day prior to Visit 6 (Postoperative Day 28).

Parents/legal guardians will be trained with regard to the instillation of eye drops prior to administration of the initial dose.

Site personnel will instruct the subject's parent/legal guardian on the proper instillation of their study medication without using the study drug.

Subject's parent/legal guardian will be instructed to return the study drug at Visits 4, 5 and 6 for weighing, and for collection in the original packaging at Visit 6 or early study discontinuation. Both the Investigator and the subjects will be masked to the study drug assignment.

4.3.1 Storage Requirements

All clinical trial material will be stored in an area free of environmental extremes, avoiding excessive heat. Clinical trial material should be stored upright at 15-25°C (59-77°F). A daily temperature log will be maintained at the site. The storage location at the clinical sites will have limited access.

Subject's parent/legal guardian must be instructed regarding proper storage.

4.4 Other Materials

Additional materials (eg, scales) will be provided by the Sponsor, depending on the requirements by the site.

4.5 Packaging and Labeling

The test and control articles will be packaged and labeled in a manner consistent with the study design. All investigational products will be labeled and supplied by the Sponsor. The test article will be manufactured and filled (5-mL) into 10-mL, white, low density polyethylene (LDPE) bottles with pink polypropylene caps by Bausch & Lomb Incorporated (Tampa, FL). The control article, Prednisolone Acetate Ophthalmic Suspension, 1%, will be sourced from readily available commercial supply. The control article will be provided in 10-mL industry standard ophthalmic bottles.

The investigational products will be packaged and labeled in a manner consistent with the study design. Investigational products will be provided in kit boxes (one study kit per subject) each with two dropper bottles containing sufficient doses for duration of treatment. Supply labeling will minimally include the protocol number, kit identification number, product description, directions for use, storage conditions, caution statement, and Sponsor information. Labeling for European sites will follow the requirements of the EU Directive 2001/20/EC (Annex 13).

Subject kit boxes and subject-specific reserve kit boxes will be labeled with a 2-part, tear-off masked label. The left part of the label will remain affixed to the subject kit. Upon dispensing, the right portion of the label, which contains hidden drug information, will be detached and placed in the subject's source document.

Subject supplies will be labeled according to a computer-generated randomization scheme. The medication will be identified as a new drug, limited by federal law, EU Directive, and AP local regulation to investigational use, and appropriately labeled for investigational use for this age group.

4.6 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 are to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. In order to assess compliance of administration, subject's parent/legal guardian will be instructed to record the date and time of each study drug administration on a diary provided by the Sponsor. Site personnel will dispense diaries and the unmasked designee will weigh study drug (each bottle) before dispensing at Visit 2. Subjects should bring their study diaries and study drug (both bottles) to Visits 3 through 6. Site personnel will review the diaries and the unmasked designee will weigh the study drug (each bottle) at Visits 3 through 6 to assess compliance.

During the course of the study, the Investigator's unmasked designee must maintain an inventory of all study drug, dispensed to or returned by the subject, including subject identifiers.

At time points throughout the study and/or upon completion of the study, the Sponsor/Sponsor's representative will review and verify the Investigator's accountability

records. Following verification, and as directed by the Sponsor, all used, unused and returned product must be returned to the Sponsor at the address provided on t he Personnel and Facilities page, or with the Sponsor's permission, disposed of at the site in an appropriate manner.

4.7 Masking/Unmasking

The Investigator, subject/subject's parent/legal guardian, and Sponsor personnel involved in the monitoring or conduct of the study will be masked to the study drug. The randomization list will be produced prior to study enrollment by an unmasked statistician not otherwise involved in the study. Although the test and active comparator bottles will be visibly different, attempts will be made to mask the subjects by removing commercial labeling, replacing with identical investigational labels, and packaging in identical kit boxes. An unmasked designee will be able to view both test and comparator bottles as part of their study activities and are therefore considered as unmasked although the designee will not have access to the randomization code. The unmasked designee will be responsible for instilling the first drop after surgery, and dispensing, weighing and collecting the test articles. The unmasked designee will not be responsible for any study assessments for this study. Site Monitors will be able to monitor subject diaries and accountability records but will not be able to reconcile the bottles in the boxes with the accountability records.

The Investigator must contact the Medical Monitor prior to unmasking of study treatment. In an emergency situation, however, where knowledge of the study treatment is critical to subject safety, the code may be broken. If unmasking is necessary, the masked section of the two-part label, which is placed in the subject's source documentation, can be scratched off to reveal the treatment assignment for that subject.

The Investigator must notify the Medical Monitor and/or Study Manager as soon as possible after unmasking. In addition, the Investigator must record the date, time, and reason for unmasking the study treatment in the source documentation.

4.8 Methods of Assigning Subjects to Treatment Groups

4.8.1 Treatment Allocation

Study drug will be allocated to eligible subjects at Visit 2, which will be the day the subject has undergone routine, uncomplicated surgery for childhood cataract. Each enrolled subject will receive sufficient study drug for the duration of treatment (ie, two bottles). The unmasked designee will dispense the next sequential kit number and administer the first dose after surgery.

4.8.2 Treatment Replacement

Reserve supplies of each subject's study drug (ie, one bottle) will be provided to the Investigators, to be dispensed only if the original subject kit is lost, damaged, or consumed prior to the end of treatment.

4.9 Risk Assessment

Refer to the Investigator's Brochure provided by the Sponsor which includes a summary of data and guidance for the Investigator in regards to the clinical pharmacology and safety profile of LE.

The subject's parent/legal guardian will be informed of any risks in the ICF.

4.10 Selection of Dose

The dose regimen in this study is the same regimen across both treatment groups (ie, 1 to 2 drops of study drug instilled in the study eye, QID, at approximately 4 hour intervals). This regimen was selected for the study based on the dose regimen of the currently marketed *Lotemax* (LE Ophthalmic Gel, 0.5%) and is also the treatment recommended in the Package Insert (PI) and Summary of Product Characteristics (SmPC) of the comparator drug.

Based on the standard of care for the treatment of postoperative inflammation in the US, both treatment groups will be dosed QID for the first 14 days and then tapered to BID from postoperative days 15 through 21 and the further tapered to QD from postoperative day 22 until the day prior to Visit 6 (Postoperative Day 28).

5.0 STUDY METHODS

5.1 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's parent/legal guardian. The subject's/subject's parent/legal guardian willingness and ability to meet the follow-up requirements of the study will be determined. If the subject's parent/legal guardian chooses to participate in the investigation, then the subject's assent (when applicable and according to local regulations) and written informed consent will be obtained. The subject's parent/legal guardian and the person obtaining written consent will sign and date the IRB/EC-approved ICF. The original signed document will be retained in the subject records, and a copy will be provided to the subject's parent/legal guardian. In addition, the applicable privacy regulation requirements must be met.

5.1.1 Visit 1 (Screening, Day -15 ±14 days)

Visit 1 will proceed as follows:

NOTE: All ocular assessments and VA will be performed bilaterally.

- obtain assent (when applicable), written informed consent (US, EU, and AP) and HIPAA authorization (US only)
- determine if the subject meets preliminary eligibility criteria:
  - documentation of demographic information
  - current and relevant medical and ophthalmic history
  - concomitant medications
- if the subject meets the preliminary eligibility criteria, the following assessments will be performed:
  - ocular symptoms

- pediatric visual acuity (VA) testing
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy

NOTE: Surgery will be scheduled to occur within 29 days of the Screening Visit. Screening and surgery cannot take place on the same day.

5.1.2 Visit 2 (Surgery/Randomization, Day 0 [within 29 days of screening])

Visit 2 will proceed as follows:

NOTE: All ocular assessments and VA will be performed bilaterally.

- record adverse events (AEs) and changes in concomitant medications
- pediatric VA assessment
- biomicroscopy
- IOP measurement
- fundoscopy, if performed during surgery, if not, then perform at Visit 3
- immediately following surgery, determine eligibility

NOTE: Subjects who, in the Investigator's opinion, have surgical complications such that it is not in their best interest to continue in the study are considered screen failures and will not be randomized into the trial.
If during the surgery it is determined that additional manipulations, such as pupil stretching or the use of iris hooks are required, it is left to the Investigator's discretion whether or not it is safe to randomize the subject into the trial.
At the conclusion of the surgery, no subconjunctival or intracameral steroid injections are permitted. If a steroid injection is deemed necessary by the Investigator, the subject cannot be randomized and is considered a screen failure.

- randomize eligible subjects by assigning the next sequential subject kit box
- the unmasked designee must weigh both bottles of study drug prior to dispensing
- at the conclusion of surgery, the randomized subject will receive the first dose of study drug from the unmasked designee followed by an antibiotic of the Investigator's choice and an eye patch
- study drug will be dispensed to the subject's parent/legal guardian by the unmasked designee
- a study drug administration diary will be provided to the subject's parent/legal guardian who will be instructed to record the time of each instillation and to bring the diary and study drug (both bottles) to each visit. The subject's parent/legal guardian will be reminded that no other information should be recorded in the diary
- the subject's parent/legal guardian will be trained by site personnel with regard to the correct instillation of eye drops prior to administration of the initial dose at any time at Visit 1 or 2 without using the study drug, but prior to their first instillation of study drug outside of the office. The time and method is left to the Investigator's discretion
- either the unmasked designee or the subject's parent/legal guardian will administer approximately one to two drops of study drug into the lower cul-de-sac of the study

eye in the evening, after removing the patch and before applying the shield, which will cover the study eye overnight

- the subject's parent/legal guardian will proceed with administration of the study drug on the morning of the first postoperative day with QID dosing at approximately four hour intervals, independently of when Visit 3 is scheduled to occur

5.1.3 Visit 3 (Postoperative Day 1; First Calendar Day after Surgery)

At Visit 3, the following assessments will be performed:

NOTE: All ocular assessments and VA will be performed bilaterally.

- AEs and changes in concomitant medications
- the unmasked designee must weigh both bottles of study drug
- ocular symptoms
- pediatric VA
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy.

NOTE: If, at any time point after surgery, IOP is elevated, treatment or intervention is left to the Investigator's discretion and the subject is to continue the study.

- fundoscopy, if not performed during surgery

NOTE: Topical antibiotic drops should be administered at least 15 m inutes AFTER study drug application.

- review and collect study drug administration diary for compliance. Instruct subject's parent/legal guardian to record time of each instillation on the diary and to bring the diary and study drug (both bottles) to their next visit. Remind subjects that no other information should be recorded in the diary
- dispense new diary
- the unmasked designee must redispense study drug
- instruct subject's parent/legal guardian to continue dosing the study drug QID, at approximately four hour intervals for the next 2 weeks

5.1.4 Visit 4 (Postoperative Day 7, ±2 days)

At Visit 4, the following assessments will be performed:

NOTE: All ocular assessments and VA will be performed bilaterally.

- AEs and changes in concomitant medications
- the unmasked designee must weigh both bottles of study drug
- ocular symptoms
- pediatric VA
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy

- review study drug administration diary for compliance. Instruct subject's parent/legal guardian to record time of each instillation in the diary and to bring the diary and study drug (both bottles) to their next visit. Remind subject's parent/legal guardian that no other information should be recorded in the diary
- dispense new diary
- the unmasked designee must redispense study drug
- remind subject's parent/legal guardian that the dosing is QID for another week and then BID for one week

5.1.5 Visit 5 (Postoperative Day 14, ±3 days)

At Visit 5, the following assessments will be performed:

NOTE: All ocular assessments and VA will be performed bilaterally.

- AEs and changes in concomitant medications
- the unmasked designee must weigh both bottles of study drug
- ocular symptoms
- pediatric VA
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy

- fundoscopy (it is at the Investigator's discretion whether to perform fundoscopy with or without mydriasis)
- review study drug administration diary for compliance. Instruct subject's parent/legal guardian to record time of each instillation in the diary and to bring the diary and study drug (both bottles) to their next visit. Remind subject's parent/legal guardian that no other information should be recorded in the diary
- dispense diary
- the unmasked designee must re-dispense study drug
- remind subject's parent/legal guardian that the dosing is BID for the rest of the week and QD for the last week

5.1.6 Visit 6 (Postoperative Day 28, ±7 days; End of Treatment)

At Visit 6, the following assessments will be performed:

NOTE: All ocular assessments and VA will be performed bilaterally.

- AEs and changes in concomitant medications
- the unmasked designee must weigh both bottles of study drug and collect all used and unused study drug (both bottles)
- collect diaries

- ocular symptoms
- pediatric VA
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy

5.1.7 Visit 7 (Postoperative Day 42, ±7 days)

At Visit 7, the following assessments will be performed:

NOTE: All ocular assessments and VA will be performed bilaterally.

- AEs and changes in concomitant medications
- ocular symptoms
- pediatric VA
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy

5.1.8 Visit 8 (Postoperative Day 90, ±14 days; Study Exit)

At Visit 8, the following assessments will be performed:

NOTE: All ocular assessments and VA will be performed bilaterally.

- AEs and changes in concomitant medications
- ocular symptoms
- pediatric VA
- biomicroscopy
- IOP measurement

NOTE: Measurement of IOP must occur after the assessment of ocular symptoms, VA and biomicroscopy

- fundoscopy (it is at the Investigator's discretion whether to perform fundoscopy with or without mydriasis)
- subject exits from study

5.1.9 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 during a given visit timeframe, the data from the visit that is intended to meet the 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.

5.1.10 Missed Visits

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

5.2 Post-study Follow-up

If a subject requires further follow-up of AEs upon discontinuation or completion of the study, the Investigator must schedule post-study follow-up visits, as necessary. Refer to Sections 6.3 and 6.4 for follow-up of AEs following study exit.

5.3 Study Completion

Depending on local regulations, Bausch + Lomb Global Clinical Operations will notify the Investigator when to contact the IRB/EC to inform them that the study is complete or Bausch + Lomb will do this on the behalf of the Investigator. In the EU, Bausch + Lomb will inform the regulatory agencies in the concerned member states in addition.

5.3.1 Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely or placed on hold, appropriate notification will be given to the Investigator(s), IRB/EC, FDA, and appropriate EU regulatory agencies, as applicable. Bausch + Lomb Global Clinical Operations will instruct the Investigators to stop/restart dispensing study materials and will arrange for study closeout, if applicable, at each site.

5.4 Concomitant Medications/Therapy

Administration of all medications used by the subject, the breastfeeding mother, or wet nurse up to 30 days prior to study entry (date ICF signed) through study exit must be recorded in the source documentation and in the Concomitant Medications eCRF. Indications for these medications should be recorded in the subject's Medical History eCRF, as applicable.

5.4.1 Permitted Therapy

Permitted therapy applies to the subject, breastfeeding mother, or wet nurse. Use of topical antibiotics is allowed if they are not used in combination with any steroid in the study eye (eg, Zylet® or TobraDex should not be used). Topical antibiotics used preoperatively and postoperatively are allowed bilaterally and must be recorded in the Concomitant Medications eCRF provided by the Sponsor. Intraoperative use of topical antibiotics or other standard of care surgical medications should be recorded in the source documentation only.

In the event that the subject requires surgery on the contralateral eye at any time during the study, the fellow eye will be treated at the Investigator's discretion with standard of care medication. The standard of care medication must be recorded under concomitant medications in the eCRF provided by the sponsor.

With the exception of the disallowed medications in Section 5.4.2, any medications that, in the Investigator's judgment, will not interfere with the study parameters are allowed to be used concurrently by the subject, breastfeeding mother, or wet nurse; for example, the following medications are permitted:

- systemic analgesics (eg, acetaminophen/paracetamol)
- oral birth control pills
- ≤100 mg/day acetylsalicylic acid (for breastfeeding mother/wet nurse only)
- hypoglycemic agents
- anticholesterol medications
- insulin
- systemic antimicrobials
- antidepressants
- thyroid preparations
- antihypertensive agents
- cardiovascular agents

  - Standard anesthetic and mydriatic agents may be used intraoperatively or for postoperative diagnostic purposes (ie, IOP and funduscopy). Ocular NSAIDs may not be used for mydriasis or at any other time point during the study in the study eye. Ocular therapy with NSAIDs and/or corticosteroids in the fellow eye is permitted.
  - The long term use of systemic NSAIDs is not allowed during the study. If unavoidable, use of systemic NSAIDs can be permitted only after Visit 5, but should be kept to a minimum and treatment duration with NSAIDs should be kept short (for example, one day per treatment period).
  - Topical ocular hypotensive agents, if used at the end of surgery by the study site, will be used with ALL subjects treated at that site.
  - Intracameral injection of antibiotic is allowed at the end of surgery.

5.4.2 Disallowed Therapy

A disallowed medication could be administered in an emergency if the subject's safety was in jeopardy. The Investigator must notify the Medical Monitor as soon as possible after administering a disallowed medication to verify if the subject can continue in the study. If a subject has taken any disallowed medication, this should be recorded as a protocol deviation. Disallowed therapy that is used for persistent or worsening inflammation, however, is called "Rescue Therapy" and is discussed in detail in Section 3.2.3.

Disallowed medications include the following:

- Ocular (study eye):
  - corticosteroids
  - NSAIDs
  - topical antibiotic-steroid combination products (eg, Zylet, TobraDex, etc)
- Ocular (study and fellow eye):
  - mast cell stabilizers
  - antihistamines

  - decongestants
  - immunosuppressants (eg, Restasis)
- Systemic (subject, breastfeeding mother, or wet nurse):
  - corticosteroids (except corticosteroid inhalers and dermatological corticosteroids, as long as they are not used on the eyelids or surrounding area)
  - NSAIDs (short term use of systemic NSAIDs is permitted only after Visit 5. Please refer to section 5.4.1 for details)
  - immunosuppressants
- Any medication that the Investigator feels may interfere with study parameters

5.5 Treatment Compliance

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

5.6 Protocol Deviations

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

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

6.0 ADVERSE EVENTS

6.1 Definition of Adverse Events

- Any untoward medical occurrence in a subject participating in a clinical study which does not necessarily have a causal relationship with the study 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.

6.2 Definition of Serious Adverse Events

Information about every serious adverse event (SAE) will be collected and recorded. An SAE is any untoward medical occurrence (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

As above, 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. Hospitalization in the absence of a medical AE is not in itself an AE. For example, the following reports of hospitalization without a medical AE should not be considered either serious, or an AE:

- 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)
- social admission (eg, subject has no place to sleep)
- administrative admission (eg, for yearly physical exam)
- optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery)

6.3 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's parent/legal guardian gives informed consent until the last study visit, Visit 8 (Postoperative Day 90). The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The Investigator or designee will elicit reports of AEs from the subject/subject's parent/legal guardian at each study visit and record all AEs. An assessment of all AEs will be made by the Investigator as to the severity, action taken with study treatment, and causal relationship to study drug.

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" to the study drug, an alternative etiology (ie, concomitant drug, medical history, prior AE, or other source as indicated) must be provided.

The subject's parent/legal guardian will be instructed to contact the Investigator immediately if any unusual systemic or ocular AEs are noticed between visits.

Additional assessments/visits may be scheduled, as necessary, to ensure the safety of the subject, during the study period. A subject who discontinues due to an AE should be seen for post-study follow-up visits as necessary.

Non-serious AEs that are ongoing upon early discontinuation or at the study exit visit will be followed by the Investigator up to 30 days after the subject exits the study.

6.4 Reporting Serious Adverse Events and Follow-up

Any SAE must be reported to Bausch + Lomb Global Safety & Vigilance; independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced from consent through the Exit Visit (Visit 8, Postoperative Day 90) must be reported to Bausch + Lomb regardless of the relationship to the study drug. After the Exit Visit (Visit 8, Postoperative Day 90), or following early discontinuation from the study, only SAEs considered related to the study drug should be reported promptly. For US sites, these should be reported to Bausch + Lomb Global Safety & Vigilance; for EU sites, these should be reported to the EU Study Manager who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance; for AP sites, these should be reported to Bausch + Lomb AP Global Safety & Vigilance (Seoul, Korea), who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance (Madison, NJ, US). Within 24 hours of notification the Investigator will fax a completed Serious Adverse Event Report to the Bausch + Lomb contact noted below. For SAEs with fatal outcomes, a summary of available autopsy findings should be submitted as soon as possible.

Bausch + Lomb Contact Information:

Name of Contact	**Contact Information**
US Sites: Saberi Rana Ali, MBBS, MS (Ophth), MPH Associate Director, Global Safety and Vigilance Bausch & Lomb Incorporated 7 Giralda Farms, Suite 1001 Madison, NJ 07940 US	Tel: +1 973 360 6478 Fax: +1 813 975 7750 Mobile: +1 862 579 8366 SAE Inbox: SAE@bausch.com

EU Sites: Natasa Orlic-Pleyer, MD Clinical Study Manager Dr. Gerhard Mann chem.-pharm. Fabrik GmbH/Bausch & Lomb Brunsbütteler Damm 165-173 13581 Berlin Germany	Tel. +49 (0) 30 33093 -318 Fax: + 49 (0) 30 33093 6699 Email: natasa.orlic-pleyer@bausch.com
AP Sites: Bausch + Lomb Asia Pacific Global Safety and Vigilance Bausch & Lomb Korea 13F, KT&G Kosmo Daechi-Tower, #945-10 Daechi-dong, Gangnam-gu, Seoul 135-280, Korea	Tel: + 82 70 7167 9784 Mobile: + 82 10 9112 9784 Fax: + 82 2 6442 1460 Email: safety.asia@bausch.com

The Investigator or Bausch + Lomb, as appropriate for local regulations, will notify their IRB/EC in writing of any SAE in accordance with the IRB/EC requirements.

Bausch + Lomb or its designee will be responsible for submitting SAE reports to regulatory authorities based on applicable regulations. The Sponsor will also send a notification to all participating Investigators of any SAE that is unexpected and associated with the study (refer to Section 6.5). This notification will be made within 15 calendar days from the time Bausch + Lomb becomes aware of the event.

If the Investigator becomes aware of any new information regarding a Serious Adverse Event (ie, resolution, change in condition, or new treatment), a new Serious Adverse Event Form must be completed and faxed to Bausch + Lomb (refer to contact information above) as soon as new information becomes available. The original SAE form is not to be altered. The report should 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. For US sites, the events and endpoints will be reported in writing by the Investigator to Bausch + Lomb Global Safety & Vigilance; for the EU sites, the SAE form should be sent to the EU Study Manager who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance; for AP sites, these should be reported to Bausch + Lomb AP Global Safety & Vigilance (Seoul, Korea), who will be responsible for forwarding to Bausch + Lomb Global Safety & Vigilance (Madison, NJ, US).

Following the subject's discontinuation or completion of the study, for any timeframe afterward deemed medically significant, any SAEs, which are assessed as causally related to study drug, should also be reported to Bausch + Lomb Global Safety & Vigilance.

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

Any Suspected Unexpected Serious Adverse Reaction (SUSAR) or unexpected SAE related to a subject's participation in the study, regardless if the study drug was administered, warrants 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 (CIOMS I Form), or relevant reporting form for the global region. Where relevant, 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 Bausch + Lomb Global Safety & Vigilance, the site Investigator must submit the expedited safety report to the local IRB/EC and for EU sites the Sponsor will submit them to the EC and health authorities within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The site principal Investigators must retain a complete copy of each expedited safety report as it was submitted to the IRB/EC. It is important that the principal Investigators review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

6.6 Medical Monitor

The Medical Monitor information is as follows:

Name of Contact	Contact Information
James Gow, MD Clinical Affairs Bausch & Lomb Incorporated 50 Technology Drive Irvine, CA 92618-2301 US	Tel: + 1 949 788 5359 Mobile: + 1 949 701 6398 Email: james.gow@bausch.com

7.0 STATISTICAL METHODS

7.1 Study Endpoints

7.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the mean grade of anterior chamber inflammation at Visit 5 (Postoperative Day 14). For each subject, the mean grade of anterior chamber inflammation will be derived using the following table:

Anterior Chamber Inflammation Grade	Slit lamp	Penlight with handheld magnifying 20 diopter lens
Grade 0 = None	Grades 0 cells and flare	Grade 0
Grade 1 = Mild	Maximum of cells and flare Grade is 1	Grade 1
Grade 2 = Moderate	Maximum of cells and flare Grade is 2	Grade 2
Grade 3 = Severe	Maximum of cells and flare Grade is 3	Grade 3
Grade 4 = Very Severe	Maximum of cells and flare Grade is 4	Grade 4

7.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- mean grade of anterior chamber inflammation at Visits 4 and 6 (Postoperative Days 7 and 28)

- proportion of subjects with Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 converted anterior chamber inflammation at each visit (Postoperative Days 7, 14, and 28)
- presence/absence and total area, if present, of synechiae at each visit (Postoperative Days 7, 14, and 28)
- presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28)

7.1.3 Safety Endpoints

The safety endpoints are as follows:

- incidence of overall and specific AEs
- type and incidence of AEs at each visit
- change in IOP from baseline (Visit 2, Surgery/Randomization) to each visit
- greatest IOP change from baseline - including the measurement at Visit 3 (Postoperative Day 1)
- greatest IOP change from baseline - excluding the measurement at Visit 3 (Postoperative Day 1)
- ocular signs (biomicroscopic examination of the lids, conjunctiva, cornea, anterior chamber without pupil dilation) at each visit

7.1.4 Tolerability Endpoints

The tolerability endpoint is as follows:

- ocular symptoms (photophobia) at each visit

7.2 Hypotheses

Test for the non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1% will be primarily based on the following one-sided null hypothesis (H_o) and alternative hypothesis (H_a):

$$H_o: \mu_{LE} - \mu_{PR} \geq 0.35 \quad \text{versus} \quad H_a: \mu_{LE} - \mu_{PR} < 0.35$$

where μ_{LE} and μ_{PR} are the mean grade of anterior chamber inflammation at Visit 4 (Postoperative Day 7) for LE Ophthalmic Gel, 0.5% and Prednisolone Acetate Ophthalmic Suspension, 1% treatment group, respectively.

7.3 Sample Size

A sample size of 120 subjects (60 subjects per treatment group) yields 98% power to detect non-inferiority of LE Ophthalmic Gel, 0.5% to Prednisolone Acetate Ophthalmic Suspension, 1%. This sample size assumes a common standard deviation of 0.47, a two-sided alpha=0.05, a non-inferiority margin of 0.35 and an expected difference of 0 for the difference in means between treatment groups using anterior chamber inflammation at Visit 5 (Postoperative Day 14). Assuming a subject dropout rate (including the initiation of rescue medication) of 12%, approximately 140 subjects will be randomized, of which at least 60 subjects will be in the age group 0-3 years as per the FDA's Written Request.

The power and sample size calculations were done using nQuery Advisor version 7.0.

7.4 Randomization

A total of 140 subjects from ages 0-11 will be randomized to receive LE Ophthalmic Gel, 0.5% or Prednisolone Acetate Ophthalmic Suspension, 1% in a 1:1 ratio. The subgroup age 0-3 years will consist of at least 60 subjects.

7.5 Analysis Populations

The analysis populations that will be used in this study are:

- Intent-to-Treat (ITT) Population: includes all subjects who were randomized and have at least one post-treatment assessment. Analysis on the ITT population will be used for primary efficacy analyses and will be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized.
- Per Protocol (PP) Population: includes all of the subjects in the ITT population that remained in the study through Visit 5 (Postoperative Day 14) and who did not deviate from the protocol in any way likely to seriously affect the primary outcome of the study. Analysis using the PP population will be used to supplement the ITT analysis, analyzing subjects according to the treatment received.
- Safety Set: includes all participants who received at least one dose of study drug.

7.6 Statistical Analysis

7.6.1 Methods of Analysis

Summaries for continuous variables will include the sample size, mean, standard deviation (SD), median, minimum, and maximum. Summaries for discrete variables will include the tabulation of frequencies and percentages. Means and medians will be presented to one more decimal place than the recorded data. Standard deviations will be presented to two more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. Confidence intervals (CIs) will be presented using the same number of decimal places as the parameters (eg, mean). Percentages will be presented to one decimal place.

The primary efficacy analysis will be based on the ITT population with missing data imputed using the last observation carried forward (LOCF) method and the primary endpoint mean grade of anterior chamber inflammation at Visit 5 (Postoperative Day 14). The mean grade of anterior chamber inflammation at Visit 5 (Postoperative Day 14) will be analyzed using an analysis of variance (ANOVA) model with treatment as a classification variable.

The least squares mean for each treatment group, the difference in the least squares mean between the two treatment groups (LE Ophthalmic Gel, 0.5% – Prednisolone Acetate Ophthalmic Suspension, 1%), and the two-sided 95% confidence interval for the difference will be presented. The null hypothesis will be rejected and non-inferiority established if the upper limit of the confidence interval does not exceed0.35.

To supplement the primary analyses, the analyses above will be repeated for the PP population; no imputation will be conducted for missing data. Any discrepancy between the ITT and PP analyses will be explained.

The secondary efficacy analyses will be conducted based on the ITT population as well as the PP population.

As a secondary analysis, the analysis of the mean grade of anterior chamber inflammation will be repeated as above for Visits 4 and 6 (Postoperative Days 7 and 28, respectively).

Additional secondary analyses include:

- the proportion of subjects with anterior chamber inflammation of Grade 0, Grade 1, Grade 2, Grade 3, and Grade 4 for each visit (Postoperative Days 7, 14, and 28)
- the proportion of subjects with presence/absence and total area, if present, of synechiae for each visit (Postoperative Days 7, 14, and 28)
- the proportion of subjects with presence/absence and total number, if present, of precipitates on the implant and cornea at each visit (Postoperative Days 7, 14, and 28)

For each of the above endpoints, treatment groups will be compared using the Pearson Chi-squared test or fisher's exact test as appropriate. Differences between the proportions of treatment groups and 95% confidence interval about the differences will be presented.

Subgroup analyses will be performed for anterior chamber inflammation, anterior chamber cells, and anterior chamber flare as appropriate by method of assessment (slit lamp versus penlight with handheld magnifying 20 diopter lens), country (region), age group, IOL implantation, and iris color.

All subjects in the safety set will be included in the safety analyses. Intraocular pressure will be summarized by visit using continuous summaries (including change from baseline and change from screening) for the following items:

- change in IOP from baseline (Visit 2, Surgery/Randomization) to each visit
- greatest IOP change from baseline - including the measurement at Visit 3 (Postoperative Day 1)
- greatest IOP change from baseline - excluding the measurement at Visit 3 (Postoperative Day 1)
- ocular signs (biomicroscopic examination of the lids, conjunctiva, cornea, anterior chamber without pupil dilation)

Treatment emergent systemic AEs will be summarized using discrete summaries at the subject and event level by system organ class and preferred term for each treatment group. Treatment emergent ocular AEs will be summarized for treated eyes and fellow eyes separately. Similarly, treatment emergent AEs will be summarized by severity and relationship separately. All AEs will be coded using a MedDRA dictionary (the most current version available at the start of the study will be used).

Ocular symptoms will be summarized using discrete summary statistics by visit and treatment group. These data will be summarized under the safety analyses.

7.6.2 Subject Demographics and Baseline Characteristics

Subject demographics: race, gender, and age will be summarized using discrete summary statistics. Age will also be presented using continuous summary statistics.

7.6.3 Subject Disposition

A disposition of subjects includes the number and percentage of subjects in each of the following categories:

- subjects randomized (ITT population)

- subjects treated (Safety population)
- subjects in the PP population

Within each of the previous categories, the number and percentage of subjects who completed and discontinued from the study will be summarized. The primary reason for study discontinuation described in Section 3.2.4 will also be summarized.

7.6.4 Protocol Deviations

The number of subjects within each type of protocol deviations will be presented using listings and discrete summary statistics as appropriate.

7.6.5 Treatment Compliance

Treatment compliance will be assessed as the percentage of prescribed instillations received and will be presented using discrete summary statistics in the following categories: (≤ 50%, 51-60%, 61-70%, 71-80%, 81-120%, and > 120%). Percentages will be calculated out of the number of subjects who returned diaries from that dosing period. The number and percentage of subjects in each compliance rate category will be presented.

7.6.6 Treatment Exposure

Extent of 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. Subjects who fail to return all bottles dispensed will be excluded from this summary. The extent of exposure will be summarized using continuous summary statistics.

7.6.7 Missing Data

For the primary efficacy endpoint analyzed using the ITT population, missing data and data from subjects placed on r escue medication will be imputed using the LOCF methodology. For the PP analysis, missing data and data from subjects placed on rescue medication will not be imputed.

8.0 DATA QUALITY ASSURANCE

8.1 Study Monitoring

Bausch + Lomb Global Clinical Operations representatives must be allowed to visit all study site locations to assess the data, quality, and study integrity in a manner consistent with applicable health authority regulations and the procedures adopted by the Bausch + Lomb Global Clinical Operations Department.

Prior to the start of the study, member(s) of the Bausch + Lomb Global Clinical Operations Department (or designees) will review the protocol, eCRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub-Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, 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, including adequate study documentation
- the facilities remain acceptable
- the Investigator and site personnel remains qualified and able to conduct the study
- test article accountability

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the Sponsor's actions.

8.2 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. 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 are also considered source data. Designated site personnel will pre-record appropriate dates of study drug administration and subject identifiers (initials and/or study number) on the diary. With this exception, only subject's parents/legal guardians 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 Investigator or designee should review subject completed forms during study visits. If an entry is found to be illegible or a mistake is found (eg, incorrect year was recorded), the subject's parent/legal guardian should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, and dating and initialing (US and AP only)/writing year of birth to acknowledge (EU only) the change.

8.3 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 electronically via an electronic data capture system to Bausch + Lomb Global Clinical Operations for quality assurance review, data entry, and statistical analysis.

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

8.4 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. 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 the Sponsor. 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/EC approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB/EC annual study review
- IRB/EC correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- regulatory documents (eg, financial disclosure and delegation of authority forms)
- all source documents
- copy of eCRFs
- subject's signed ICF
- FDA Form 1572
- accountability records for the test article(s)
- correspondence from and to the Sponsor
- any other documents relevant to the conduct of the study

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

8.5 Auditing Procedures

Audits of clinical research activities in accordance with the Sponsor'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/EC, the Investigator must inform the Sponsor immediately that this request has been made.

8.6 Institutional Review Board/Ethics Committee Approval

In the US and AP, the Investigator, or in the EU, the Sponsor or designee 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/EC, or if not using their institution's IRB/EC, approved by the reviewing central IRB/EC prior to entering any subjects in the study. Documentation of IRB/EC approval of the study protocol and informed consent must be provided to the Sponsor prior to initiation of the study. In addition, in the US and AP, the Investigator, or in the EU, the Sponsor or designee must ensure that the reviewing IRB/EC 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 the Sponsor and the IRB/EC prior to implementation.

8.7 Publication of Results

All study data generated as a result of this study will be regarded as confidential, until appropriate analysis and review by the Sponsor 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 the Sponsor, 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 the Sponsor 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 Incorporated products and activities receive fair, accurate, and reasonable presentation.

9.0 REFERENCES

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[2] Becker, B., Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol* 4: 198-205, 1965.

[3] Armaly, M.F. Effects of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. *Arch Ophthalmol* 70: 482, 1963.

[4] Burde, R.M., Becker, B. Corticosteroid-induced glaucoma and cataracts in contact lens wearers. *JAMA* 1970; 213: 2075-2078.

[5] Sheppard, J., Bartlett, J. Loteprednol Etabonate in Ocular Inflammation. *US Ophthalmic Review* [Extract]. Spring 2011; 4(1):1-7.

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[7] Novack, G.D., Howes, J., Crockett, R.S., Sherwood, M.B. Change in intraocular pressure during long-term use of loteprednol etabonate. *Glaucoma* 7:266-269, 1998.

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[9] Bausch + Lomb Incorporated. Clinical Study Report #577: A Randomized, Multicenter, Double-Masked, Parallel-Group Clinical Safety and Efficacy Evaluation of Loteprednol Etabonate Ophthalmic Gel, 0.5% versus Vehicle for the Treatment of Inflammation and Pain Following Cataract Surgery, v1.0. 28 Feb 2011.

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. Furthermore, all ocular signs must be evaluated by an ophthalmologist.

PROCEDURE/ASSESSMENTS[1]	**Visit 1** Screening	**Visit 2** Surgery/Randomization /Begin Treatment	**Visit 3** Follow-up	**Visit 4** Follow-up	**Visit 5** Follow-up	**Visit 6** Follow-up/End Treatment	**Visit 7** Follow-up	**Visit 8** Study Exit
	Day -15 (±14 days)	Day 0[2]	Day 1[3]	Day 7 (±2 days)	Day 14 (±3 days)	Day 28 (±7 days)	Day 42 (±7 days)	Day 90 (±14 days)
Informed consent, assent (when applicable), and authorization as appropriate for local privacy regulations	**X**							
Demographic data	**X**							
Current and relevant medical and ocular history	**X**							
Ocular symptoms	**X**		**X**	**X**	**X**	**X**	**X**	**X**
VA assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Slit lamp (biomicroscopy or magnifying lens with penlight)[4]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
IOP (Goldman or equivalent)[4]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Fundoscopy[5]		**X**	**X**		**X**			**X**
Eligibility determination	**X**	**X**						
Randomization		**X**						
AEs[6]/Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Weigh study drug and inspect diaries		**X**	**X**	**X**	**X**	**X**		
Dispense study drug and diaries		**X**[7]	**X**	**X**	**X**			
Collect study drug and diaries						**X**		
Exit subject								**X**

[1] All ophthalmic assessments will be performed bilaterally.
[2] Visit 2 must occur within 29 days of Visit 1. Screening and surgery cannot take place on the same day.
[3] Visit 3 (postoperative day 1) should occur on the next calendar day post-surgery.
[4] Every effort should be made to obtain slit lamp assessments and the assessment with the 20 dpt magnifying lens and penlight should only be performed if a slit lamp or handheld slit lamp examination cannot be performed. Once one of the methods has been chosen it should be employed throughout the study for each subject. IOP should also be measured with the same method throughout the study for each subject.
[5] Fundoscopy will be performed bilaterally either at Visit 2 (surgery/randomization) or Visit 3 (postoperative day 1), at Visit 5 (postoperative day 14 ±3 days), and at Visit 8 (postoperative day 90 ±14 days).
[6] Collection of AEs extends from the time the subject's parent/guardian signs informed consent until the last study visit.
[7] The subject's parent/legal guardian will be trained with regard to the correct instillation of eye drops without using study drug prior to their administration of the initial dose.

APPENDIX B: METHODS OF CLINICAL EVALUATION

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

All ophthalmic assessments will be performed bilaterally at all visits.

1. PEDIATRIC VISUAL ACUITY

Whenever possible best corrected (if applicable) Snellen distance VA will be measured in both eyes. Otherwise, the Investigator will attempt the following techniques in sequential order:

1. Single Letter VA (eg, HOTV, Sheridan Gardiner, Tumbling E)
2. Picture VA (eg, Allen, Lea)
3. Visual Behavior (eg, fix and follow, cover test)

Whenever possible, the same VA testing method should be employed for all study visits for each subject.

2. BIOMICROSCOPY

- To be performed by an ophthalmologist
- Use of fixed or handheld slit lamp or ophthalmic operating microscope is preferred
- Use of a penlight with a 20 dpt magnifying lens is permitted if slit lamp examination is not possible
- Method needs to be indicated in eCRF, the same method should be used throughout the study for each subject
- If the anterior chamber is assessed with a slit lamp, a high power field slit beam of 1 mm x 1 mm is to be used

Ocular Tearing: Assess degree of ocular tearing.

0 = Absent	Normal tear production.
1 = Mild	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 runny nose.

Ocular Discharge: Assess degree of 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 the eyelids in the morning upon awakening
2 = Moderate	Moderate amount of mucopurulent or purulent discharge is noted in the lower cul-de-sac. Frank matting together of the eyelids in the morning upon awakening
3 = Severe	Profuse amount of mucopurulent or purulent discharge is noted in the lower cul-de-sac and in the marginal tear strip. Eyelids tightly matted together in the morning upon awakening, requiring warm soaks to pry the lids apart

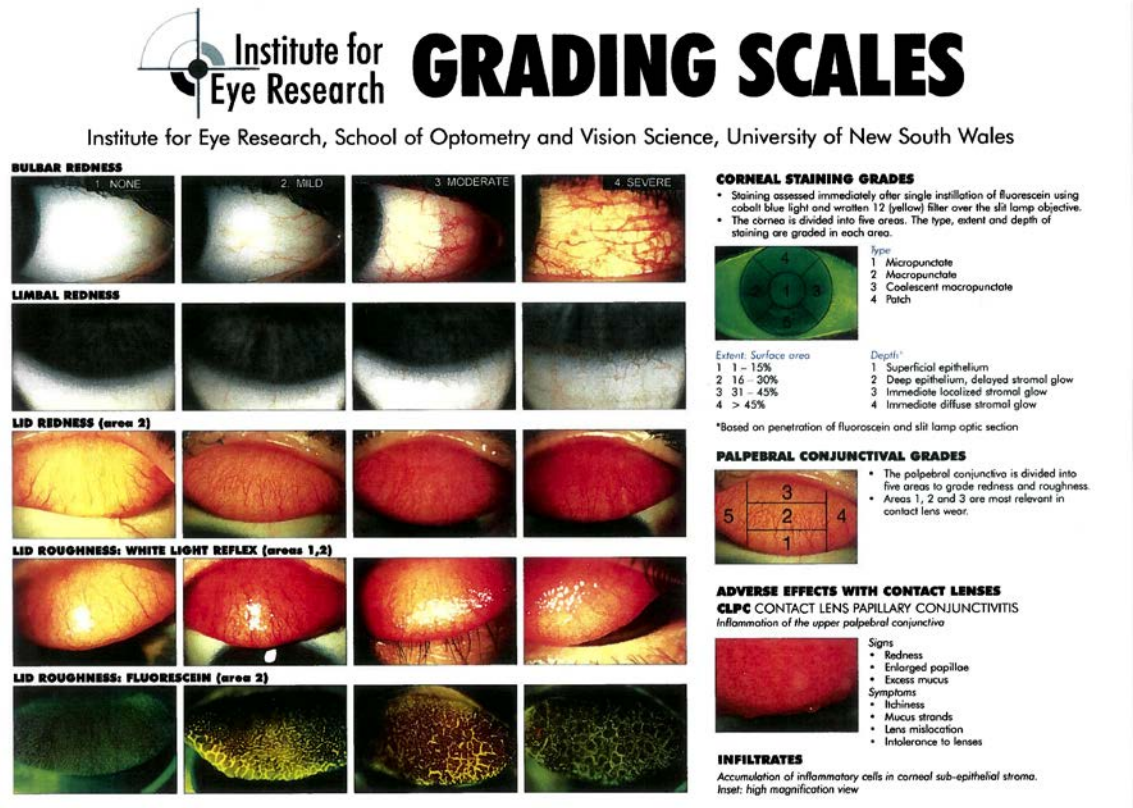
Conjunctival Chemosis: Assess swelling of the conjunctiva.

0 = Absent	No edema
1 = Mild	Edema present in one 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 Conjunctival Injection: Assess redness and swelling from dilated blood vessels in the bulbar conjunctiva.

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

Standardized Photographs for Grading Bulbar Conjunctival Injection:



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

0 = Absent

1 = Present

Hyphema: Assess presence or absence of hyphema.

0 = Absent

1 = Present

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

Anterior Chamber Cells (for those subjects that can be examined with a slit lamp): Assess accumulation of white blood cells in aqueous. Pigment cells and red blood cells are to be ignored. Assess anterior chamber using a high power field slit beam of 1 mm x 1 mm.

0 = No cells seen

1 = 1 - 5 cells

2 = 6 - 15 cells

3 = 16 - 30 cells

4 = >30 cells

Anterior Chamber Flare (for those subjects that can be examined with a slit lamp): 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

Anterior Chamber Inflammation (for subjects that can only be examined with a pen light and a 20 dpt magnifying lens):

0 = None	Clear anterior chamber with no visible clouding (Tyndall effect and cells combined). Red reflex normal
1 = Mild	Mild anterior chamber clouding. Clear iris pattern on visualization. Red reflex normal
2 = Moderate	Moderate anterior chamber clouding
3 = Severe	Severe anterior chamber clouding. Iris pattern not clearly visualized. Red reflex diminished
4 = Very severe	Severe anterior chamber clouding with a white and/or milky appearance of the anterior chamber. Red reflex absent or severely diminished

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

0 = Absent

1 = Present*

*If present, indicate the total area of synechiae in full clock hours.

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

0 = Absent

1 = Present*

*If present, indicate the total number of the precipitates.

Hypopyon: Assess presence or absence of hypopyon.

0= Absent

1= Present

3. INTRAOCULAR PRESSURE

- Evaluated by an ophthalmologist
- Preferred methods: Goldmann or Perkins
- If Goldmann or Perkins are not possible: Tono-Pen or rebound (Icare)
- For each subject, the same method should be used throughout the study
- Well calibrated (monthly, at minimum) measuring instruments will be used to measure IOP

4. FUNDOSCOPY

- Bilateral fundus exam at Visit 2 (Surgery/Randomization) or Visit 3 (Postoperative Day 1), at Visit 5 (Postoperative Day 14), and at Visit 8 (Study Exit)
- Fundoscopy can be performed either via direct ophthalmoscopy (ophthalmoscope) or indirect ophthalmoscopy (either slit lamp or with a penlight and handheld 20 dpt lens)
- It is at the Investigator's discretion whether fundoscopy is done with dilated or undilated pupils
- Mydriatic drugs should only be administered after all vision testing is complete
- NSAIDs cannot be used as a mydriatic agent

Posterior pole: Assess for abnormalities in the posterior pole.

0 = Normal

1 = Abnormal

Optic Nerve: Assess for abnormalities in the optic nerve.

0 = Normal

1 = Abnormal

Cup/Disc Ratio: Assess the cup/disc ratio. The largest cup to disc ratio measured should be entered on the eCRF.

5. OCULAR SYMPTOMS

Photophobia:

0 = Absent	Absence of positive sensation. (For babies, a normal reaction to any light source.)
1 = Mild	Very minimal light intolerance which may require some degree of sunglass protection to eliminate the symptom, noticed primarily in sunlight. (For babies, a normal reaction to room light but more squinting or discomfort is shown to brighter room light or sunlight than normal reaction.)
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. (For babies, discomfort at normal room light is shown and more comfort is shown in dimly lit environments.)
3 = Severe	Constant or nearly constant exquisite 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 severe enough to commonly require bed rest and, in some instances, systemic sedation. (For babies, squinting of the eyes or crying at any light source is shown and only total occlusion seems comforting.)