CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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Table of Contents

STATISTICAL REVIEW AND EVALUATION 1

1 EXECUTIVE SUMMARY 4

2 INTRODUCTION 6

2.1 OVERVIEW 6
2.2 DATA SOURCES 7

3 STATISTICAL EVALUATION 7

3.1 DATA AND ANALYSIS QUALITY 8
3.2 EVALUATION OF EFFICACY 8
3.2.1 Study Design and Endpoints 8
3.2.2 Patient Disposition, Demographic and Baseline Characteristics 10
3.2.3 Statistical Methodologies 14
3.2.4 Results and Conclusions 15
3.3 EVALUATION OF SAFETY 20

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 20

4.1 GENDER, RACE, AND AGE 20
4.2 EFFECT OF BASELINE PAIN AND CELL SCORE 21

5 SUMMARY AND CONCLUSIONS 27

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE 27
5.2 CONCLUSIONS AND RECOMMENDATIONS 27

APPENDIX 30

5.3 DETAILED RESULTS ON ANTERIOR CHAMBER CELL AND RESCUE MEDICATION 30
5.4 DETAILED RESULTS ON PAIN RESOLUTION AND RESCUE MEDICATION 31
5.5 APPLICANT'S RESULTS ON AGE SUBGROUPS 33
5.6 OBSERVED VERSUS IMPUTED ANTERIOR CHAMBER CELL SCORE OVER TIME 37
5.7 ANTERIOR CHAMBER FLARE SCORE VERSUS ANTERIOR CHAMBER CELL SCORE OVER TIME 39

LIST OF TABLES

Table 1: List of All Studies Included in Analysis of Efficacy and Safety 7
Table 2: Subject Disposition and Primary Reason for Discontinuation, Study 576 11
Table 3: Subject Disposition and Primary Reason for Discontinuation, Study 577 12
Table 4: Subject Demographics- ITT Population, study 576 13
Table 5: Subject Demographics - ITT Population, study 577 14
Table 6: Anterior Chamber Cell Resolution Over Time 17
Table 7: Pain Resolution Over Time, Post-surgery 19
Table 8: Treatment Effect on Cell Resolution at Day 8 in Different Subgroups, Study 576 23
Table 9: Treatment Effect on Cell Resolution at Day 8 in Different Subgroups, Study 577 23
Table 10: Treatment Effect on Pain Resolution at Day 8 in Different Subgroups, Study 576 26
Table 11: Treatment Effect on Pain Resolution at Day 8 in Different Subgroups, Study 577 26
Table 12: Count and Rates of Different Response Categories for Anterior Chamber Cell in Study 576 30
Table 13: Count and Rates of Different Response Categories for Anterior Chamber Cell in Study 577 31
Table 14: Count and Rates of Different Response Categories for Pain in Study 576 32
Table 15: Count and Rates of Different Response Categories for Pain in Study 577 33
Table 16: Primary Efficacy Analysis by Study and Age, Age < 65 subgroup, Study 576 34
Table 17: Primary Efficacy Analysis by Study and Age, Age>=65 to <75, Study 576 34
Table 18: Primary Efficacy Analysis by Study and Age, Age>=75, Study 576 35
Table 19: Primary Efficacy Analysis by Study and Age, Age <65, Study 577 35
Table 20: Primary Efficacy Analysis by Study and Age, Age>=65 to <75, Study 577 36
Table 21: Primary Efficacy Analysis by Study and Age, Age >=75, Study 577 36
Table 22: Mean Anterior Chamber Cell Score Over Time, Observed and LOCF 38

LIST OF FIGURES

Figure 1: Cell Flare Resolution Over Time, Post-surgery 16
Figure 2: Ocular Pain Resolution Over Time, Post-Surgery 18
Figure 3: Difference in Resolution Rates of Anterior Chamber Cell at Day 8 in Study 576 for Different Subgroups 22
Figure 4: Difference in Resolution Rates of Anterior Chamber Cell at Day 8 in Study 577 for Different Subgroups 22
Figure 5: Difference in Resolution Rates of Pain at Day 8 in Study 576 for Different Subgroups 25
Figure 6: Difference in Resolution Rates of Pain at Day 8 in Study 577 for Different Subgroups 25
Figure 7: Observed versus Imputed (LOCF) Anterior Chamber Cell Values Over Time 38
Figure 8: Scatter Plot of Observed Cell Score on Observed Flare Score by visit and study, LE Gel 0.5% Treatment Group 39
Figure 9: Scatter Plot of Observed Cell Score on Observed Flare Score by visit and study, Vehicle Treatment Group 40

1 EXECUTIVE SUMMARY

This NDA submission for Loteprednol etabonate 0.5% gel (LE gel 0.5%) dosed four times daily for 14 days, for the indication of resolution of pain and inflammation following ocular surgery. The Applicant submitted the results of two pivotal trials measuring inflammation and pain following cataract surgery to support this indication.

The active ingredient in LE gel 0.5% is a corticosteroid. This same active ingredient is in two other approved products developed for the same indication by the same applicant. Loteprednol etabonate 0.5% ophthalmic suspension or Lotemax ® has been approved since 1998 for multiple indications including treatment of inflammation following ocular surgery (NDA 20583). Loteprednol etabonate 0.5% ointment has been approved in 2009 for treatment of inflammation and pain following ocular surgery (NDA 200738).

The two studies, Study 576 and Study 577 supporting this application are randomized, multicenter, placebo controlled trials. Each study had two arms, a placebo arm and an active control arm (LE gel 0.5%), with a one to one randomization. Most subjects in the two trials are from US sites. That is, all 406 subjects in Study 576 and 391 out of 407 subjects in Study 577 are from US. The remaining 16 subjects in Subject 577 are from Germany.

Two primary efficacy endpoints were assessed at day 8 post-surgery: complete resolution (without rescue medication) of anterior chamber cell inflammation and complete resolution (without rescue medication) of pain. Anterior chamber cell inflammation is quantified by investigators in a 5-point grade scale (0 to 4) whereas ocular pain is assessed by patient and recorded by investigator in a 6-point grade scale (0 to 5). Complete resolution for each scale is defined as a grade of 0. In both endpoints, receiving rescue medication anytime before study visit is considered a treatment failure.

Based on the primary efficacy results as well as supportive analysis of secondary endpoints, we recommend approval of the product. The efficacy results on primary endpoint are summarized in the table below for proposed label. For proportion of anterior chamber cell resolution under treatment in randomized subjects, the effect size is 15% with 95% confidence interval of (6%, 23%) in study 576 and it is 17% with 95% confidence interval of (9%, 26%) in study 577. For proportion of ocular pain resolution under treatment in randomized subjects, the effect size is 31% with 95% confidence interval of (21%, 41%) in study 576 and 30% with 95% confidence interval of (20%, 39%) in study 577. Other exploratory analyses in the review support the efficacy claims by Applicant.

We propose the following changes for the label in Section 8.5 Geriatric Use and Section 14 Clinical Studies. If the differences between age groups are determined to be clinically significant, we recommend the following wording for Section 8.5 of the labeling which incorporates the subgroup findings

8.5 Geriatric Use
In the two clinical trials, older subjects (71 years or above) had smaller treatment effect than younger subjects (70 years or below).

In the Clinical Studies section, our following wording provide a more precise description of subjects recruited in the trial (Anterior Chamber Cell inflammation and Ocular Pain at baseline), a more precise definition of primary endpoints, and present results on the primary endpoints in a Table. This table is the reviewer's table reproducing the Applicant's results.

14 CLINICAL STUDIES

In two independent, randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 813 subjects with an anterior chamber cells of 6 cells or above after cataract surgery, TRADENAME was more effective compared to its vehicle for treatment of post-operative inflammation and ocular pain following cataract surgery.

Primary endpoints were complete resolution of anterior chamber cells (cell count of 0 and no rescue medication) and complete resolution of ocular pain (ocular pain grade of 0 and no rescue medication) at post-operative day 8.

Table: Efficacy Results in Clinical Studies for TRADENAME

Response at Day 8 Post Surgery	Treatment		Study 1	Study 2
Anterior Chamber Cell Resolution[1] with no Rescue Medication	TRADENAME	n/N (%)	62/203 (31%)	64/206 (31%)
	Vehicle	n/N (%)	33/203 (16%)	28/201 (14%)
	Difference (95% CI [3])		15% (6%, 23%)	17% (9%, 26%)
No Ocular Pain[2] and no rescue medication [1]	TRADENAME	n/N (%)	148/203 (73%)	156/206 (76%)
	Vehicle	n/N (%)	85/203 (42%)	92/201 (46%)
	Difference (95% CI [3])		31% (21%, 41%)	30% (20%, 39%)

[1] Anterior Chamber cell resolution is cell count of zero. At baseline (post-surgery day 1), all subjects had 6 cells or above
[2] No ocular Pain is a pain grade of zero. At baseline (post-surgery day 1), about 50% of subjects suffered from ocular pain.
[3] 95% CI is 95% confidence interval using asymptotic normality assumption.

2 INTRODUCTION

This application is for the approval of Loteprednol etabonate ophthalmic gel 0.5% (LE gel 0.5%), dosed four times daily (QID) for 14 days, for the indication of pain and inflammation following ocular surgery. The ocular surgery model used in the submitted trials is cataract surgery.

This section gives a brief overview of other available drugs for this indication, including drugs with same active ingredient. Then, this section summarizes the design of the two vehicle control studies submitted in this application. Finally, a list of reviewed material with link to datasets is provided.

2.1 Overview

There are many products currently available for this indication, either corticosteroids or Non-steroidal anti-inflammatory drugs (NSAID). The active ingredient in this gel, Loteprednol etabonate 0.5%, is a corticosteroid. This same active ingredient is in two other approved products developed for the same indication by the same applicant. Loteprednol etabonate 0.5% ophthalmic suspension or Lotemax® has been approved since 1998 for multiple indications including treatment of inflammation following ocular surgery (NDA 20583). Loteprednol etabonate 0.5% ointment has been approved in 2009 for treatment of inflammation and pain following ocular surgery (NDA 200738).

Two identically planned studies are used to support this indication: study 576 and 577. The two studies are randomized, multicenter, placebo controlled trials. Each study had two arms, a placebo arm and an active control arm (LE gel 0.5%), with a one to one randomization.

Most subjects in the two trials are from US sites. Study 576 with 406 subjects was entirely in the US. Study 577 with 407 subjects had 20 centers in the US recruiting 391 subjects and 2 centers in Germany with only 16 subjects.

The main information on the two clinical studies is summarized in the following Table.

Table 1: List of All Studies Included in Analysis of Efficacy and Safety

Study	Dose	Treatment Period	Centers	# of Subjects per Arm	Study Population
576 randomized, multicenter parallel arm study	QID for 14 days	14 days post-cataract surgery	17 sites in US	(1) Loteprednol Etabonate gel (203 subjects) (2) Vehicle (203 subjects)	Subjects who underwent cataract surgery
577 randomized, multicenter parallel arm study	QID for 14 days	14 days post-cataract surgery	22 sites, 20 in US and 2 in Germany	(1)Loteprednol Etabonate gel (206 subjects) (2)Vehicle (201 subjects)	Subjects who underwent cataract surgery

2.2 Data Sources

This NDA submission is electronic. The link for submission's study reports and datasets is at \\cdsesub1\EVSPROD\NDA202872\0002\m5

The original application was for [redacted] (b) (4)

The integrated summary of efficacy has a listing of tables but no written summary of the results. Individual clinical study reports have details on protocol, results and interpretation of the efficacy and safety results. However, efficacy tables for different subgroups are only in the integrated summary of efficacy and they are not reported in the individual clinical study report.

3 STATISTICAL EVALUATION

This statistical review focuses on efficacy as there are no major safety concerns with this product.

In this section, we first comment on the data and analysis quality, then show our evaluation of efficacy. We reproduced the Applicant's results for the primary endpoints and added our own exploratory analyses for a better understanding of the results. Unless

otherwise stated, all tables and figures in this Section are those produced by the primary reviewer.

3.1 Data and Analysis Quality

We were able to reproduce the Applicant's results for efficacy. The submitted data is not in SDTM format. However, the datasets and derivations are well documented in the define.pdf file and the applicant's sas code was submitted. The documentation allows for easy traceability from the case report forms to the integrated datasets. We could easily reproduce the applicant's results as well as conduct our own exploratory analyses.

Since efficacy is the main concern with the statistical review of this product, we used the dataset adeff.xpt from the integrated summary of efficacy folder (ise). In addition to identifying variables for subject and study (usubjid, studyid), this dataset has all efficacy variables (anchcell, cell.1s, ocpain, g0.pn1s) demographic variables (age, sex, race, country) and timing variables (visit, visitnum).

We derived a multi-response category outcome for pain and for inflammation to produce figures and tables in this review illustrating efficacy.

3.2 Evaluation of Efficacy

In this subsection, we first summarize the main study design features and give exact definitions for the primary and secondary endpoints. Then, we summarize the patient disposition, demographic and baseline characteristics. We briefly explain the statistical methodologies before showing our results and conclusion.

3.2.1 Study Design and Endpoints

Studies 576 and 577 have identical design with different centers. They are randomized, multicenter, placebo controlled studies. The randomization was 1:1 to either vehicle or LE gel 0.5% and was stratified by site according to a unique randomization scheme. Subject supplies' were labeled according to a computer-generated randomization schedule and dispensed sequentially by kit number within a site. Subjects were instructed to self-administer study drug, QID at approximately four hour intervals for 14 days.

Each trial has about 200 subjects in each arm. All 17 centers in study 576 are in the US. Study 577 has two centers in Germany and 20 centers in the US with centers in Germany contributing only 16 subjects.

The total duration of the study is four weeks from screening to last visit with seven scheduled visits. The screening visit (visit 1) occurs up to two weeks prior to surgery. The second visit is on surgery day. Eligibility and randomization occurs after surgery on post-operative day 1 (visit 3). Efficacy is then assessed at Post-operative days 3 (visit 4), post-

operative day 8 (visit 5), and post-operative day 15 (visit 6). A post treatment exam is also provided at post-operative day 18 (visit 7).

Subjects in the study had to satisfy some minimal entry criteria at screening (visit 1) and more extensive inclusion/exclusion criteria at post cataract-operative day 1 (visit 3) before randomization. The main inclusion/exclusion criteria are described in what follows. At screening (visit 1), adult subjects had to be undergoing uncomplicated cataract surgery [1] and in the investigator's opinion, had potential post-operative pinholed Snellen Visual Acuity (VA) of at least 20/200 in the study eye. The screening excluded those subjects who used corticosteroid within 14 days of the surgery. At visit 3 (post-operative Day 1), subjects screened into the study were eligible for randomization if they had undergone routine, uncomplicated cataract surgery and had 6 or more cells in their anterior chamber cells examination. In addition, subjects were not eligible for the study at visit 3 if they required concomitant medication such as ocular or systemic NSAIDs, corticosteroids, mast cell stabilizers, antihistamines, decongestants, or immunosuppressant therapy. Finally, subjects were not eligible if they had elevated IOP of 21mmHg or more, uncontrolled glaucoma or were being treated for glaucoma in the study eye and have Pinholded Snellen VA 20/200 or worse in the non-study eye.

Endpoints

There are two primary endpoints, one assessing inflammation resolution and the other assessing ocular pain resolution. Inflammation was assessed by investigator's anterior chamber cells 5-point grade scale (0 to 4). Ocular pain was assessed by patients and recorded by the investigator in a 6-point grade scale (0 to 5).

The investigator's instructions for grading anterior chamber cells are as follows: "Use a high-power field slit beam of 1 mm x 1 mm. Assess accumulation of white blood cells in aqueous. Pigment cells and red blood cells are to be ignored. 0 = No cells seen, 1 = 1 - 5 cells, 2 = 6 – 15 cells, 3 = 16 - 30 cells, and 4 = >30 cells."

Ocular Pain was defined in the protocol as a positive sensation of the eye, including foreign body sensation, stabbing, throbbing, or aching. It was graded from 0-5 as follows "0 = None; Absence of positive sensation. 1 = Minimal; Presence of mild sensation or discomfort typical of postoperative ocular surgery (eg, diffuse or focal foreign body sensation, mild transient burning or stinging, etc.) 2 = Mild; Tolerable aching of the eye. 3 = Moderate; Moderate or more prolonged aching sufficient to require the use of over the counter (OTC) analgesics (eg, acetaminophen). 4 = Moderately Severe; More prolonged aching requiring the use of an OTC analgesic other than acetaminophen. 5 = Severe; Intense ocular, periocular or radiating pain (eg, constant or nearly constant sharp stabbing pain, throbbing or aching, etc.) requiring prescription analgesics."

[1] Defined as phacoemulsification with posterior chamber intraocular lens implantation, not combined with any other surgery

The two primary endpoints are responder endpoints assessed at visit 5 (post-operative day 8). They are defined as follows

1- Complete resolution of anterior chamber cells at visit 5 (post-operative day 8). This endpoint measures resolution of inflammation and is a composite endpoint of cell score of 0 at visit 5 **and** no need for rescue medication at visit 5 or anytime before.
2- Complete resolution of pain at visit 5 (post-operative day 8). This endpoint measures resolution of pain and is a composite endpoint of pain score of 0 at visit 5 **and** no need for rescue medication at visit 5 or anytime before.

Thus, for both endpoints, subjects taking rescue medication are treated as failures.

Note that the inclusion criteria for being randomized into the study is to have a grade 2 or more of anterior chamber cell score at visit 3 (post-operative day 1). There is no inclusion criterion on ocular pain score at visit 3.

The secondary efficacy endpoints measure supportive evidence of inflammation and pain and their resolution over time. They are defined as

1- Complete resolution (Grade 0 pain) at each visit and for each study eye's final on treatment visit.
2- Complete resolution of anterior chamber flare (Grade 0 flair) at each visit and for each study eye's final on treatment visit
3- Complete resolution of anterior chamber cells and flare (Grade 0 of cells and Grade 0 of flare) at each visit and for each study eye's final on treatment visit
4- Change from baseline to each follow-up visit in anterior chamber cells and anterior chamber flare combined and separately

Anterior chamber flare was also graded by investigator in 5-point grade scale (0 to 4)The protocol instructions for the grading of flare are: "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."

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition and discontinuation are shown in Table 2 for Study 576 and Table 3 for Study 577. We see in these tables that both studies had a few subjects receiving a different treatment than the one they were randomized to (6 subjects in Study 576 and 10 subjects in Study 577). These mistakes in treatment assignment were restricted to three sites in Study 576 and two sites in Study 577. In addition, we see that both studies had a minimal number of discontinuations, (6/406) in Study 576 and (3/407) in Study 577.

Table 2: Subject Disposition and Primary Reason for Discontinuation, Study 576

(Source: Applicant's Table 4 in Study 576 study report)

Disposition and Discontinuation	LE Gel N(%)	Vehicle N(%)	Overall N(%)
Total Number of Subjects Randomized	203	203	406
Treated	203 (100.0%)	203 (100.0%)	406 (100.0%)
As Randomized	200 (98.5%)	200 (98.5%)	400 (98.5%)
Not As Randomized[1]	3 (1.5%)	3 (1.5%)	6 (1.5%)
Included in Safety Population	203 (100.0%)	203 (100.0%)	406 (100.0%)
Completed[2]	199 (98.0%)	198 (97.5%)	397 (97.8%)
Discontinued	4 (2.0%)	5 (2.5%)	9 (2.2%)
Included in ITT Population	203 (100.0%)	203 (100.0%)	406 (100.0%)
Completed[2]	199 (98.0%)	198 (97.5%)	397 (97.8%)
Discontinued	4 (2.0%)	5 (2.5%)	9 (2.2%)
Included in Per Protocol (PP) Population	194 (95.6%)	194 (95.6%)	388 (95.6%)
Completed[2]	191 (98.5%)	191 (98.5%)	382 (98.5%)
Discontinued	3 (1.5%)	3 (1.5%)	6 (1.5%)
Primary Reason for Discontinuation			
Withdrawal by subject	2 (1.0%)	1 (0.5%)	3 (0.7%)
Adverse event	1 (0.5%)	1 (0.5%)	2 (0.5%)
Investigator decision	0	1 (0.5%)	1 (0.2%)
Other	1 (0.5%)	2 (1.0%)	3 (0.7%)

[1] There were 6 randomization errors in three different sites. One subject from each site was assigned to vehicle but received LE Gel, and one subject from each site was assigned to LE Gel but received vehicle.
[2] Percentages for completed and discontinued subjects were based on the number of subjects in the population being summarized.

Table 3: Subject Disposition and Primary Reason for Discontinuation, Study 577
(Source: Applicant's Table 4 in Study 577 report)

Disposition and Discontinuation	LE Gel N(%)	Vehicle N(%)	Overall N(%)
Total Number of Subjects Randomized	206	201	407
Treated	206 (100.0%)	201 (100.0%)	407 (100.0%)
As Randomized	201 (97.6%)	196 (97.5%)	397 (97.5%)
Not As Randomized[1]	5 (2.4%)	5 (2.5%)	10 (2.5%)
Included in Safety Population	206 (100.0%)	201 (100.0%)	407 (100.0%)
Completed[2]	204 (99.0%)	196 (97.5%)	400 (98.3%)
Discontinued	2 (1.0%)	5 (2.5%)	7 (1.7%)
Included in ITT Population	206 (100.0%)	201 (100.0%)	407 (100.0%)
Completed[2]	204 (99.0%)	196 (97.5%)	400 (98.3%)
Discontinued	2 (1.0%)	5 (2.5%)	7 (1.7%)
Included in Per Protocol (PP) Population	187 (90.8%)	186 (92.5%)	373 (91.6%)
Completed[2]	187 (100.0%)	183 (98.4%)	370 (99.2%)
Discontinued	0	3 (1.6%)	3 (0.8%)
Primary Reason for Discontinuation			
Adverse event	1 (0.5%)	1 (0.5%)	2 (0.5%)
Investigator decision	0	2 (1.0%)	2 (0.5%)
Failure to follow study procedures	0	1 (0.5%)	1 (0.2%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)

[1] There were 10 randomization errors in 2 different sites, four in one site and six in the other site. Two subjects in one site were assigned vehicle but received LE Gel, and two subjects in the same site were assigned LE Gel and received vehicle. Similarly in the other site, in each treatment group, three subjects were not assigned the treatment they were randomized to.
[2] Percentages for completed and discontinued subjects were based on the number of subjects in the population being summarized.

The demographic characteristics of subjects are similar in the two studies (shown in Table 4 for study 576 and in Table 5 for Study 577) and are balanced between the two treatment groups. The average age is about 69 years old. There were more female (57%) than male (43%) in both studies. In Study 576, the subjects are predominantly white (88%) with some black or African American subjects (9%) and few subjects from other minorities. In Study 577, the majority of subjects is also white (74%) with some black or African American subjects (11%), Asians (13%) and very few subjects from other racial groups.

We will describe the baseline values of anterior chamber cell grade and ocular pain grade in Subgroups Subsection 4.2

Table 4: Subject Demographics- ITT Population, study 576

(Source: Applicant's Table 5 in study 576 study report)

	LE Gel N(%)	Vehicle N(%)	Overall N(%)
Age (years)			
N	203	203	406
Mean ± SD	69.3 (8.73)	69.0 (9.80)	69.1 (9.27)
Median	69.0	71.0	71.0
Minimum, Maximum	50, 91	36, 88	36, 91
Race			
White	176 (86.7%)	182 (89.7%)	358 (88.2%)
Black/African American	20 (9.9%)	16 (7.9%)	36 (8.9%)
American Indian/Alaskan Native	0	1 (0.5%)	1 (0.2%)
Asian	2 (1.0%)	3 (1.5%)	5 (1.2%)
Native Hawaiian/Pacific Islander	1 (0.5%)	0	1 (0.2%)
Other race	4 (2.0%)	1 (0.5%)	5 (1.2%)
Gender			
Male	94 (46.3%)	81 (39.9%)	175 (43.1%)
Female	109 (53.7%)	122 (60.1%)	231 (56.9%)
Ethnicity			
Not Hispanic and not Latino	188 (92.6%)	189 (93.1%)	377 (92.9%)
Hispanic or Latino	15 (7.4%)	14 (6.9%)	29 (7.1%)

SD is Standard Deviation

Table 5: Subject Demographics - ITT Population, study 577
(Source: Applicant's Table 5 in study report 577)

	LE Gel N(%)	Vehicle N(%)	Overall N(%)
Age (years)			
N	206	201	407
Mean ± SD	68.3 (9.66)	69.4 (9.56)	68.9 (9.62)
Median	69.0	71.0	70.0
Minimum, Maximum	30, 89	43, 88	30, 89
Race			
White	151 (73.3%)	149 (74.1%)	300 (73.7%)
Black/African American	22 (10.7%)	21 (10.4%)	43 (10.6%)
American Indian/Alaskan Native	2 (1.0%)	2 (1.0%)	4 (1.0%)
Asian	28 (13.6%)	25 (12.4%)	53 (13.0%)
Native Hawaiian/Pacific Islander	0	0	0
Other race	3 (1.5%)	4 (2.0%)	7 (1.7%)
Gender			
Male	82 (39.8%)	92 (45.8%)	174 (42.8%)
Female	124 (60.2%)	109 (54.2%)	233 (57.2%)
Ethnicity			
Not Hispanic and not Latino	189 (91.7%)	181 (90.0%)	370 (90.9%)
Hispanic or Latino	17 (8.3%)	20 (10.0%)	37 (9.1%)
Country			
US	198 (96.1%)	193 (96.0%)	391 (96.1%)
Germany	8 (3.9%)	8 (4.0%)	16 (3.9%)

SD is Standard Deviation

3.2.3 Statistical Methodologies

Testing for efficacy on the two primary endpoints was planned as hierarchical testing. First, test superiority of LE gel 0.5% to vehicle for complete anterior chamber cells resolution on treatment at visit 5 (post-op day 8) endpoint. If that is significant, then test for superiority of LE gel to vehicle for proportion of complete ocular pain resolution on treatment at visit 5 (post-op day 8) endpoint.

The primary analysis for testing differences in proportions of responders for each of the primary endpoint uses Pearson chi-squared statistic. The secondary analysis uses Cochran Mantel-Haenszel adjusting for site. Other secondary analyses use exact methods for the primary endpoints. Confidence intervals are constructed using asymptotic methods.

We used the same methods in our analyses and derivations in the overall population. For subgroup analyses, we used wilson's method to compute 95% confidence intervals.

3.2.4 Results and Conclusions

Results of both trials suggest that LE gel 0.5% is effective at reducing inflammation and pain after ocular surgery. This conclusion is supported by the analysis on the primary endpoint as well as on the secondary endpoints and replicated in both trials. Main results of the two trials are summarized in figures at tables in this section.

Results on anterior chamber cell are shown in Figure 1 and Table 6 in this section and Table 12 and Table 13 in Appendix. The solid line in each of the four panels in Figure 1 shows the proportion of subjects who had a complete resolution of anterior chamber cell and did not receive any rescue therapy at each post-surgery visit. In both trials, the rate for the vehicle groups (solid line in top left and right panel) increases slowly over time from 0%[1] on the first day post-surgery to about 25% at the end of study, whereas the rate for the LE gel 0.5% group (solid line in bottom left and right panel) increases rapidly from 0% on the first day post-surgery to about 50% resolution rate at the end of study. We see in Table 6 that the treatment effect is significant at the primary endpoint time of assessment (day 8 post-surgery) with treatment effect and 95% confidence interval of 15% (6%, 23%) in Study 576 and 17% (9%, 26%) in Study 577. In the same table, we see also that in both trials the treatment effect nearly doubles to 25%-28% by day 15 and is maintained around 25%-26% at day 18.

The primary endpoint of inflammation resolution is a composite endpoint of complete resolution of anterior chamber cell (i.e. cell score of zero) and no rescue medication. To tease out the contribution of each of these two components, Figure 1 in this section and corresponding Table 12 and Table 13 in Appendix show the rate of two complements. Those are the proportion of subjects who received rescue medication out of all randomized subjects (solid gray line in Figure 1) and the proportion of subjects who were unresolved and did not receive rescue medication out of all randomized subjects (dashed gray line in Figure 1).

[1] Inclusion criteria is for cell grade to be 2 or above at 1 day post-surgery (baseline). Thus, the rate of subjects with no resolution at baseline is 0% for both the vehicle arm and LE gel 0.5% arm

In the two studies, LE gel 0.5% is better than vehicle in both of the two components and the rate of those receiving rescue medication have a larger impact on the observed treatment difference in the primary endpoint than the rate of those not resolving on treatment. The magnitude of contribution of these two components to the primary endpoints is slightly different in the two studies. We see in Figure 1 in this section and Table 12 and Table 13 in Appendix that the rate of those receiving rescue medications (solid gray line) is higher in the vehicle arm than in the LE gel 0.5% arm in the two studies, and the separation between the rates in the two arms occur as early as Day 8 visit. The rate of those receiving rescue medications in the vehicle arm is 34% at Day 8 visit and climbs to 69% at Day 18 visit in study 576; it is 23% at Day 8 visit and climbs to 56% at Day 18 visit in study 577. The rate of those receiving rescue medications in the LE gel 0.5% arm is lower than vehicle by 26% at Day 8 and 34% at Day 18 in Study 576 and 20% at Day 8 and 36% at Day 18 in Study 577. The rate of those unresolved is also higher in the vehicle arm than in the LE gel 0.5%, however the difference is not as large as that observed between the two treatment arms for the rescue medications groups.

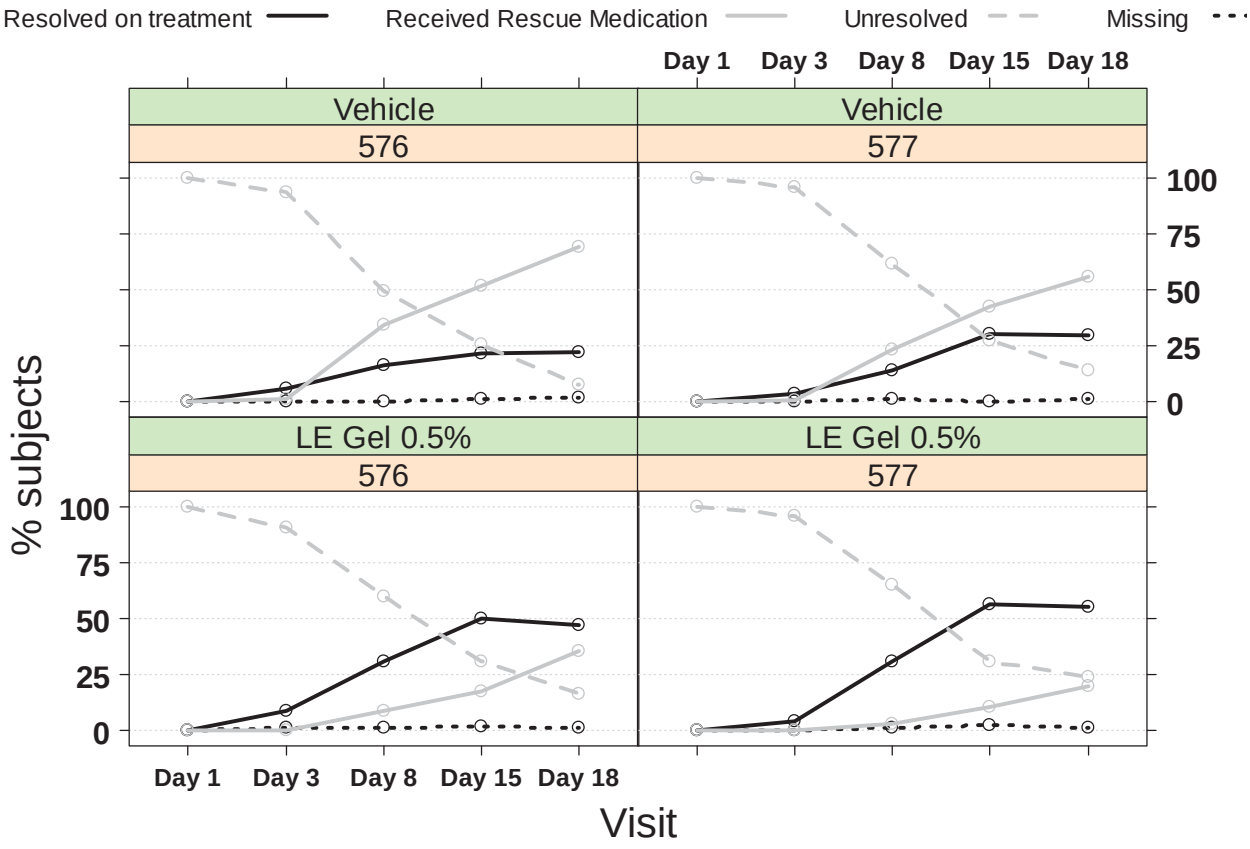

Figure 1: Cell Flare Resolution Over Time, Post-surgery

Table 6: Anterior Chamber Cell Resolution Over Time

Visits	Treatment Arms	Study 576			Study 577		
		Total ITT (N)	Resolved with No Rescue Medication		Total ITT (N)	Resolved with No Rescue Medication	
			n	n/N (%)		n	n/N (%)
Visit 3 - Post-op Day 1 (Baseline)	LE gel, 0.5%	203	0	0	206	0	0
	Vehicle	203	0	0	201	0	0
Visit 4 - Post-op Day 3	LE gel, 0.5%	203	17	8	206	8	4
	Vehicle	203	11	5	201	7	3
	Difference (95% CI[1])			3% (-2%, 8%)	Difference (95% CI[1])		0% (-4%, 4%)
Visit 5 - Post-op Day 8	LE gel, 0.5%	203	62	31	206	64	31
	Vehicle	203	33	16	201	28	14
	Difference (95% CI[1])			15% (6%, 23%)	Difference (95% CI[1])		17% (9%, 26%)
Visit 6 - Post-op Day 15	LE gel, 0.5%	203	102	50	206	116	56
	Vehicle	203	44	22	201	61	30
	Difference (95% CI[1])			28% (19%, 38%)	Difference (95% CI[1])		26% (16%, 36%)
Visit 7 - Post-op Day 18	LE gel, 0.5%	203	96	47	206	114	55
	Vehicle	203	45	22	201	59	29
	Difference (95% CI[1])			25% (16%, 35%)	Difference (95% CI[1])		26% (16%, 36%)

[1] 95% confidence intervals (95% CI) are computed using asymptotic methods.

LE gel 0.5% is also effective in resolving pain after cataract surgery. Results are shown in Figure 2 and Table 7 in this section and Table 14 and Table 15 in Appendix. In both arms and in both trials, about half of subjects had a pain score above 0 at baseline (Day 1 post surgery visit). In the vehicle arm, the proportion of subjects whose pain resolves without

rescue medication (black solid line in top two panels in Figure 2) stays around 50% until Day 8 post surgery visit and slightly declines after that in the two studies. In the LE gel 0.5% arm, the proportion of subjects whose pain resolved without rescue medication (black solid line in bottom two panels in Figure 2) increases to about 75% at Day 8 and Day 15 visits and declines slightly after that. At Day 8 visit, the difference between the two treatment arms for primary endpoint of pain resolution is almost identical in the two studies. It is 31% with 95% confidence interval of (21%, 41%) in Study 576 and 30% with 95% confidence interval of (20%, 39%) in Study 577. The treatment effect estimate remains above 30% after Day 8 visit in the two trials.

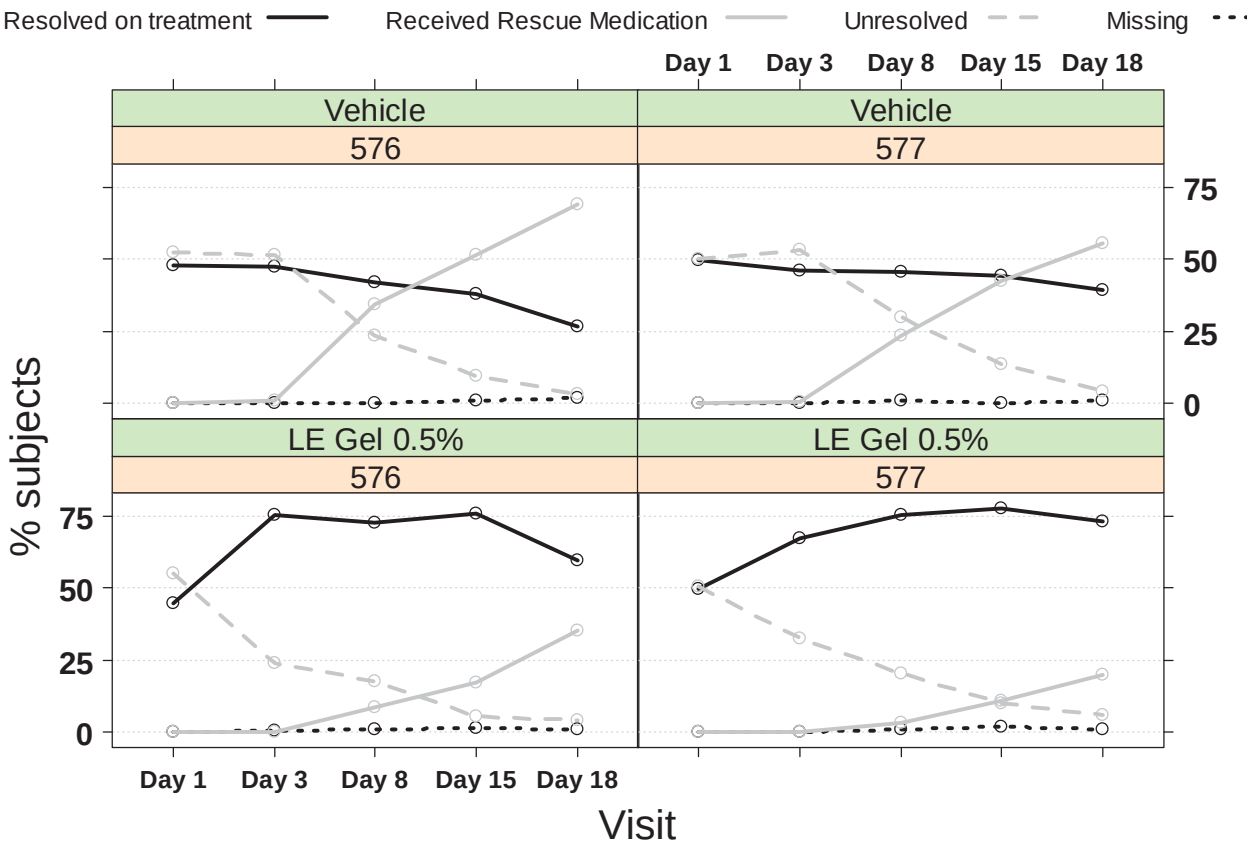

Figure 2: Ocular Pain Resolution Over Time, Post-Surgery

The primary endpoint of pain resolution is a composite endpoint of complete pain resolution (i.e. pain score of zero) and no rescue medication. To tease out the contribution of each of these two components, Figure 2 in this section and Table 14 and Table 15 in Appendix show the rate of two complements. Those are the proportion of subjects who received rescue medication out of all randomized subjects (solid gray line in Figure 2) and the proportion of subjects with unresolved pain who did not receive rescue medication out of all randomized subjects (dashed gray line in Figure 2).

Table 7: Pain Resolution Over Time, Post-surgery

Visits	Treatment Arms	Study 576			Study 577		
		Total ITT (N)	Resolved with No Rescue Medication		Total ITT (N)	Resolved with No Rescue Medication	
			n	n/N (%)		n	n/N (%)
Visit 3 - Post-op Day 1 (Baseline)	LE gel, 0.5%	203	91	45	206	102	50
	Vehicle	203	97	48	201	100	50
	Difference (95% CI[1])			-3% (-13%, 17%)	Difference (95% CI[1])		0% (-10%, 10%)
Visit 4 - Post-op Day 3	LE gel, 0.5%	203	153	75	206	139	67
	Vehicle	203	96	47	201	93	46
	Difference (95% CI[1])			28% (19%, 38%)			21% (11%, 31%)
Visit 5 - Post-op Day 8	LE gel, 0.5%	203	148	73	206	156	76
	Vehicle	203	85	42	201	92	46
	Difference (95% CI[1])			31% (21%, 41%)	Difference (95% CI[1])		30% (20%, 39%)
Visit 6 - Post-op Day 15	LE gel, 0.5%	203	154	76	206	160	78
	Vehicle	203	77	38	201	89	44
	Difference (95% CI[1])			38% (29%, 47%)	Difference (95% CI[1])		33% (24%, 43%)
Visit 7 - Post-op Day 18	LE gel, 0.5%	203	121	60	206	151	73
	Vehicle	203	54	27	201	79	39
	Difference (95% CI[1])			33% (23%, 43%)	Difference (95% CI[1])		34% (24%, 44%)

[1] 95% confidence intervals (95% CI) are computed using asymptotic methods.

In the two studies, LE gel 0.5% is better than vehicle in both of the two components and the rate of those receiving rescue medication have a larger impact on the observed treatment difference in the primary endpoint of pain resolution than the rate of those not

resolving on treatment. We already described with the results of the other primary endpoint the difference between the two treatments for the rates of those receiving rescue medications. As discussed earlier, those rates are much higher over time in the vehicle arm than in the LE gel 0.5% arm. The rate of those with unresolved pain is slightly higher in the vehicle arm than in the LE gel 0.5% (by 6% in Study 576 and 10% in Study 577) and this difference declines over time to 1%-4% difference between treatment at Day 15 and Day 18 visits. Thus, the difference between the two treatment groups for proportion of subjects with unresolved pain and no rescue medication is not as large as that observed between the two treatment arms for the proportion of subjects receiving rescue medications.

The Appendix shows the reviewer's exploratory results for secondary endpoints over time. Results in each treatment, in each study, and over time on mean anterior chamber cell score over time are shown in Appendix (Subsection 5.6). Results in each study over time of anterior chamber flare are shown in Appendix (Subsection 5.7).

3.3 Evaluation of Safety

There are no major safety concerns with this drug. Refer to the clinician's review for descriptive analysis of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The treatment effect on resolution of inflammation and pain is consistent in both studies in all subgroups by gender, race and baseline value of cell or pain. Although LE gel 0.5% is better than vehicle for all age groups, the treatment effect is smaller for the older groups than the younger groups.

The results for the first primary endpoint on inflammation resolution are shown by study in Table 8 and Table 9 and illustrated in Figure 3 and Figure 4. The results for the second primary endpoint on pain resolution are shown by study in Table 10 and Table 11 and illustrated in Figure 5 and Figure 6.

Note that in this Section, we show the results for age for the reviewer's defined four categories. The four categories of the age variable in the forest plots and the tables represent the four quartiles of the age distribution in the two studies. In this way, the number of subjects in each category is balanced. The Applicant used different age categories, their results are shown in Appendix (Subsection 5.5). Both the reviewer and the applicant's results show a similar trend for treatment effect.

4.1 Gender, Race, and Age

The magnitude of the treatment effect varied by age groups and there was a negative association between age and treatment effect for both primary endpoints. We see in Table 8 and Figure 3 for study 576 and in Table 9 and Figure 4 for study 577 that treatment

effect for primary endpoint of cell resolution with no rescue medication is 21% in Study 576 and 24% in Study 577 for those below the median age (70 years of age and below). In contrast, the treatment effect for those above the median age (71 years of age and above) is less than half that effect: 8% in Study 576 and 11% in study 576). Similarly, the treatment effect for primary endpoint of pain resolution with no rescue medication is also higher for those below the median age (70 years of age and below) compared to those above the median age (71 years of age and above). The treatment effect on ocular pain resolution for those below the median age is 35% in Study 576 and Study 577. The treatment effect on ocular pain resolution for those above the median age is 28% in Study 576 and 25% in Study 577.

The treatment effect is similar between male and female for both primary endpoints and it is significant in each subgroup. The resolution rates are similar to the rates in the overall population.

The large white subgroup shows the same treatment effect as the overall population, other subgroups show a similar trend but are often too small to make a definite conclusion. The black subgroup shows a similar trend than the overall population, but the subgroup size is too small in study 576 to make any conclusion on significance. In Study 577, the treatment effect is significant in both the white subgroup and black or African/American subgroup. The treatment effect shows positive trend for the Asian subgroup, although it is not significant due to small sample size.

4.2 Effect of Baseline Pain and Cell Score

There was no consistent effect of baseline cell score on the primary endpoint of resolution of inflammation with no rescue medication. Similarly, there was no consistent effect of baseline pain score on primary endpoint of resolution of pain with no rescue medication at day 8.

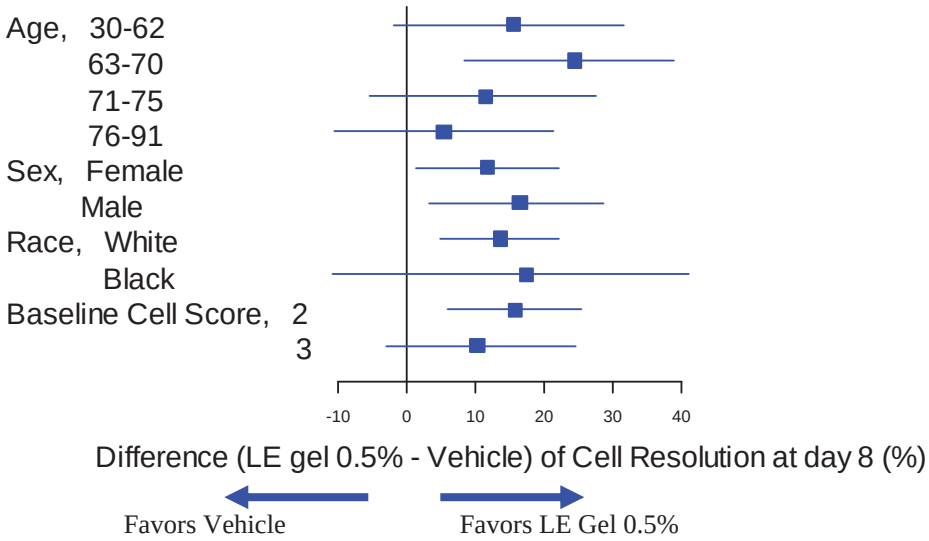

Figure 3: Difference in Resolution Rates of Anterior Chamber Cell at Day 8 in Study 576 for Different Subgroups

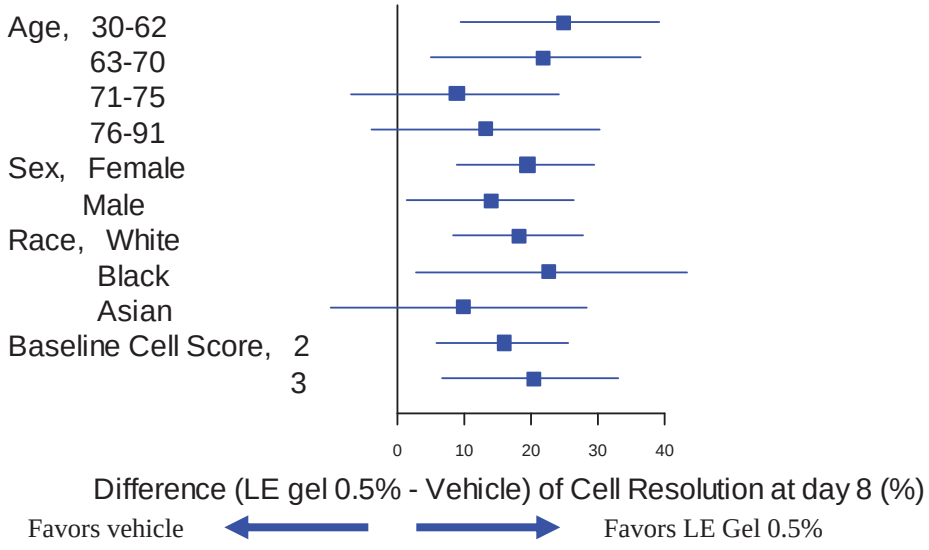

Figure 4: Difference in Resolution Rates of Anterior Chamber Cell at Day 8 in Study 577 for Different Subgroups

Table 8: Treatment Effect on Cell Resolution at Day 8 in Different Subgroups, Study 576

Study 576, overall treatment effect and 95% CI is 15% (6%, 23%)								
		Vehicle			LE GEL 0.5%			
Subgroup	Categories	N	n	n/N (%)	N	n	n/N (%)	Difference (95% CI)[1]
Age	30-62	47	8	17	49	16	33	16% (-2%, 32%)
	63-70	50	5	10	55	19	35	25% (9%, 39%)
	71-75	51	9	18	48	14	29	12% (-5%, 28%)
	76-91	55	11	20	51	13	25	5% (-10%, 21%)
Sex	Female	122	18	15	109	29	27	12% (1%, 22%)
	Male	81	15	19	94	33	35	17% (3%, 29%)
Race	White	182	30	16	176	53	30	14% (5%, 22%)
	Black	16	2	13	20	6	30	18% (-11%, 41%)
	Asian	3	1	33	2	1	50	17%
	Other	2	0	0	5	2	40	40%
Baseline Pain Score	2	148	28	19	155	54	35	16% (6%, 25%)
	3	54	4	7	45	8	18	10% (-3%, 25%)
	4	1	1	100	3	0	0	100%

Table 9: Treatment Effect on Cell Resolution at Day 8 in Different Subgroups, Study 577

Study 577, overall treatment effect and 95% CI is 17% (9%, 26%)								
		Vehicle			LE GEL 0.5%			
Subgroup	Categories	N	n	n/N (%)	N	n	n/N (%)	Difference (95% CI)[1]
Age	30-62	52	4	8	52	17	33	25% (10%, 39%)
	63-70	42	5	12	59	20	34	22% (5%, 36%)
	71-75	50	8	16	52	13	25	9% (-7%, 24%)
	76-91	57	11	19	43	14	33	13% (-4%, 30%)
Sex	Female	109	13	12	124	39	31	20% (9%, 29%)
	Male	92	15	16	82	25	30	14% (2%, 26%)
Race	White	149	25	17	151	53	35	18% (8%, 28%)
	Black	21	0	0	22	5	23	23% (3%, 43%)
	Asian	25	2	8	28	5	18	10% (-10%, 29%)
	Other	6	1	17	5	1	20	3%
Baseline Pain Score	2	148	25	17	143	47	33	16% (6%, 26%)
	3	52	3	6	61	16	26	20% (7%, 33%)

	4	1	0	0	2	1	50	50%

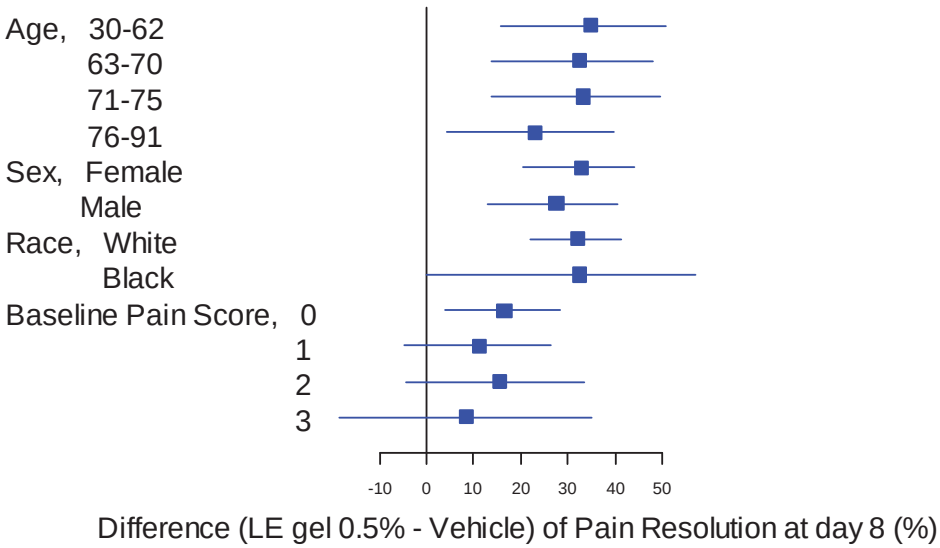

Figure 5: Difference in Resolution Rates of Pain at Day 8 in Study 576 for Different Subgroups

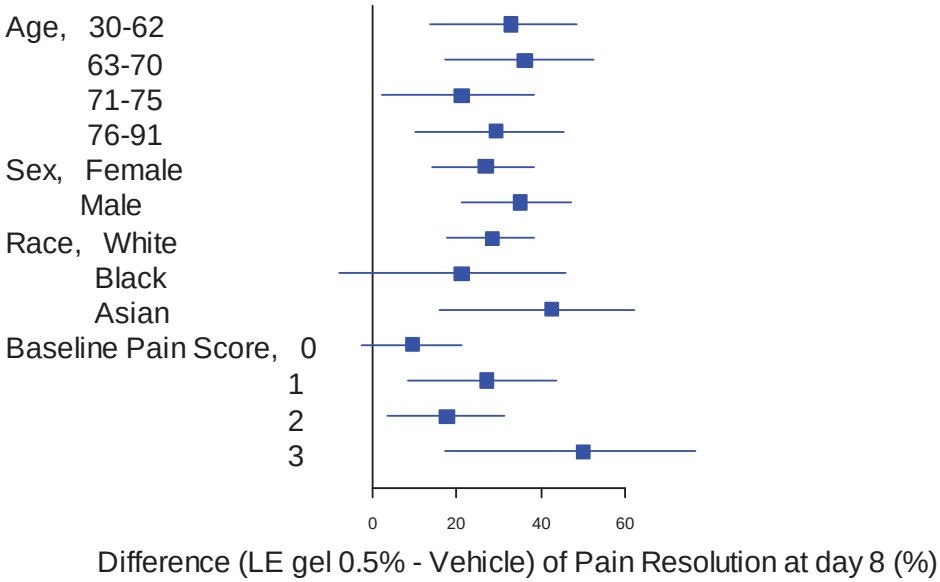

Figure 6: Difference in Resolution Rates of Pain at Day 8 in Study 577 for Different Subgroups

Table 10: Treatment Effect on Pain Resolution at Day 8 in Different Subgroups, Study 576

Study 576, overall effect and 95% Confidence Interval is 31% (21%, 41%)								
		Vehicle			LE GEL 0.5%			
Subgroup	Categories	N	n	n/N (%)	N	n	n/N (%)	Difference (95% CI)[1]
Age	30-62	47	21	45	49	39	80	35% (16%, 51%)
	63-70	50	22	44	55	42	76	32% (14%, 48%)
	71-75	51	17	33	48	32	67	33% (14%, 50%)
	76-91	55	25	45	51	35	69	23% (4%, 40%)
Sex	Female	122	47	39	109	78	72	33% (20%, 44%)
	Male	81	38	47	94	70	74	28% (13%, 41%)
Race	White	182	76	42	176	130	74	32% (22%, 41%)
	Black	16	6	38	20	14	70	29% (0%, 57%)
	Asian	3	3	100	2	1	50	-50%
	Other	2	0	0	5	3	60	60%
Baseline Pain Score	0	97	17	18	91	31	34	17% (4%, 29%)
	1	51	8	16	52	14	27	11% (-5%, 27%)
	2	33	5	15	39	12	31	15% (-4%, 33%)
	3	18	3	17	16	4	25	8% (-19%, 35%)
	4	4	0	0	4	0	0	0%
	5	0	0	0	1	1	100	100%

Table 11: Treatment Effect on Pain Resolution at Day 8 in Different Subgroups, Study 577

Study 577, overall effect and 95% Confidence Interval is 30% (20%, 39%)								
		Vehicle			LE GEL 0.5%			
Subgroup	Categories	N	n	n/N (%)	N	n	n/N (%)	Difference (95% CI)[1]
Age	30-62	52	22	42	52	39	75	33% (14%, 49%)
	63-70	42	19	45	59	48	81	36% (17%, 52%)
	71-75	50	24	48	52	36	69	21% (2%, 38%)
	76-91	57	27	47	43	33	77	29% (10%, 45%)
Sex	Female	109	48	44	124	88	71	27% (14%, 38%)
	Male	92	44	48	82	68	83	35% (21%, 47%)
Race	White	149	73	49	151	117	77	28% (18%, 38%)
	Black	21	7	33	22	12	55	21% (-8%, 46%)

	Asian	25	9	36	28	22	79	43% (16%, 62%)
	Other	6	3	50	5	5	100	50%
Baseline Pain Score	0	100	21	21	102	31	30	9% (-3%, 21%)
	1	44	6	14	44	18	41	27% (9%, 44%)
	2	37	1	3	49	10	20	18% (3%, 31%)
	3	16	0	0	10	5	50	50% (17%, 76%)
	4	4	0	0	1	0	0	0%

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues in the review of this application. The applicant demonstrated efficacy of the products against vehicle in two adequate and well controlled trials. We could easily reproduce the main efficacy results presented by Applicant.

5.2 Conclusions and Recommendations

Based on the primary efficacy results as well as supportive analysis of secondary endpoints, we recommend approval of the products. The efficacy results on primary endpoint are summarized in the table below for proposed label. For proportion of anterior chamber cell resolution and no rescue medication in randomized subjects, the effect size is 15% with 95% confidence interval of (6%, 23%) in study 576 and it is 17% with 95% confidence interval of (9%, 26%) in study 577. For proportion of ocular pain resolution and no rescue medication, the effect size is 31% with 95% confidence interval of (21%, 41%) in study 576 and 30% with 95% confidence interval of (20%, 39%) in study 577. Other exploratory analysis in the review support the efficacy claims by Applicant.

We propose the following changes for the label (Section 8.5 Geriatric Use and Section 14 Clinical Studies). Our changes incorporate results of subgroup analysis on age in the Geriatric Use. In the Clinical Studies section, our changes provide a more precise description of subjects recruited in the trial (Anterior Chamber Cell inflammation and Ocular Pain at baseline), a more precise definition of primary endpoints, and present results on the primary endpoints in a Table.

Proposed by Applicant

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

14 CLINICAL STUDIES
In two independent, randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 813 subjects with a protocol-specified threshold amount of anterior

chamber cells, TRADENAME™ was more effective compared to its vehicle for treatment of post-operative inflammation and pain following cataract surgery. Primary endpoints were complete resolution of anterior chamber cells (cell count of 0) and no pain at post-operative day 8. (b) (4)

[redacted]

Proposed changes

(b) (4)

[redacted]

Table: Primary Efficacy Results in Clinical Studies for TRADENAME

Response at Day 8 Post Surgery	Treatment		Study 1 (406 subjects)	Study 2 (407 subjects)
Anterior Chamber Cell Resolution[1] with no Rescue Medication	TRADENAME	n/N (%)	62/203 (31%)	64/206 (31%)
	Vehicle	n/N (%)	33/203 (16%)	28/201 (14%)
	Difference (95% CI [3])		15% (6%, 23%)	17% (9%, 26%)
No Ocular Pain[2] and no rescue medication	TRADENAME	n/N (%)	148/203 (73%)	156/206 (76%)
	Vehicle	n/N (%)	85/203 (42%)	92/201 (46%)
	Difference (95% CI [3])		31% (21%, 41%)	30% (20%, 39%)

[1]Anterior chamber cell resolution is cell count of zero. At baseline (post-surgery day 1), all subjects had 6 cells or above

[2] No ocular Pain is a pain grade of zero. At baseline (post-surgery day 1), about 50% of subjects suffered from ocular pain.
[3] 95% CI is 95% confidence interval using asymptotic normality assumption.

APPENDIX

5.3 Detailed results on Anterior Chamber cell and Rescue Medication

Table 12 and Table 13 show counts and rates over time for missing values, subjects with rescue medication, subjects resolved with no rescue medication and subjects unresolved with no rescue medications. These rates were used to produce Figure 1 in Subsection 3.2.4 of the review.

Table 12: Count and Rates of Different Response Categories for Anterior Chamber Cell in Study 576

Study 576										
Visits	Treatment Arms	Total ITT	Missing		Rescue Medication		Resolved with No Rescue Medication		Unresolved and No Rescue Medication	
		N	n	n/N (%)	n	n/N (%)	n	n/N (%)	n	n/N (%)
Visit 1 - Screening	LE gel, 0.5%	203	0	0	0	0	203	100	0	0
	Vehicle	203	0	0	0	0	201	99	2	1
Visit 3 - Post-op Day 1	LE gel, 0.5%	203	0	0	0	0	0	0	203	100
	Vehicle	203	0	0	0	0	0	0	203	100
Visit 4 - Post-op Day 3	LE gel, 0.5%	203	2	1	0	0	17	8	184	91
	Vehicle	203	0	0	2	1	11	5	190	94
Visit 5 - Post-op Day 8	LE gel, 0.5%	203	2	1	17	8	62	31	122	60
	Vehicle	203	0	0	70	34	33	16	100	49
Visit 6 - Post-op Day 15	LE gel, 0.5%	203	3	1	35	17	102	50	63	31
	Vehicle	203	2	1	105	52	44	22	52	26
Visit 7 - Post-op Day 18	LE gel, 0.5%	203	2	1	72	35	96	47	33	16
	Vehicle	203	3	1	140	69	45	22	15	7

Table 13: Count and Rates of Different Response Categories for Anterior Chamber Cell in Study 577

Study 577										
Visits	Treatment Arms	Total ITT	Missing		Rescue Medication		Resolved with No Rescue Medication		Unresolved and no Rescue Medication	
		N	n	n/N (%)	n	n/N (%)	n	n/N (%)	n	n/N (%)
Visit 1 - Screening	LE gel, 0.5%	206	0	0	0	0	206	100	0	0
	Vehicle	201	0	0	0	0	201	100	0	0
Visit 3 - Post-op Day 1	LE gel, 0.5%	206	0	0	0	0	0	0	206	100
	Vehicle	201	0	0	0	0	0	0	201	100
Visit 4 - Post-op Day 3	LE gel, 0.5%	206	0	0	0	0	8	4	198	96
	Vehicle	201	0	0	1	0	7	3	193	96
Visit 5 - Post-op Day 8	LE gel, 0.5%	206	2	1	6	3	64	31	134	65
	Vehicle	201	2	1	47	23	28	14	124	62
Visit 6 - Post-op Day 15	LE gel, 0.5%	206	4	2	22	11	116	56	64	31
	Vehicle	201	0	0	85	42	61	30	55	27
Visit 7 - Post-op Day 18	LE gel, 0.5%	206	2	1	41	20	114	55	49	24
	Vehicle	201	2	1	112	56	59	29	28	14

5.4 Detailed Results on Pain Resolution and Rescue Medication

Table 14 and Table 15 show counts and rates over time for missing values, subjects with rescue medication, subjects resolved with no rescue medication and subjects unresolved with no rescue medications. These rates were used to produce Figure 2 in Subsection 3.2.4 of the review.

Table 14: Count and Rates of Different Response Categories for Pain in Study 576

Study 576										
Visits	Treatment Arms	Total ITT	Missing		Rescue Medication		Resolved with No Rescue Medication		Unresolved and No Rescue Medication	
		N	n	n/N (%)	n	n/N (%)	n	n/N (%)	n	n/N (%)
Visit 1 - Screening	LE gel, 0.5%	203	0	0	0	0	198	98	5	2
	Vehicle	203	0	0	0	0	197	97	6	3
Visit 3 - Post-op Day 1	LE gel, 0.5%	203	0	0	0	0	91	45	112	55
	Vehicle	203	0	0	0	0	97	48	106	52
Visit 4 - Post-op Day 3	LE gel, 0.5%	203	1	0	0	0	153	75	49	24
	Vehicle	203	0	0	2	1	96	47	105	52
Visit 5 - Post-op Day 8	LE gel, 0.5%	203	2	1	17	8	148	73	36	18
	Vehicle	203	0	0	70	34	85	42	48	24
Visit 6 - Post-op Day 15	LE gel, 0.5%	203	3	1	35	17	154	76	11	5
	Vehicle	203	2	1	105	52	77	38	19	9
Visit 7 - Post-op Day 18	LE gel, 0.5%	203	2	1	72	35	121	60	8	4
	Vehicle	203	3	1	140	69	54	27	6	3

Table 15: Count and Rates of Different Response Categories for Pain in Study 577

Study 577										
Visits	Treatment Arms	Total ITT	Missing		Rescue Medication		Resolved with No Rescue Medication		Unresolved	
		N	n	n/N (%)	n	n/N (%)	n	n/N (%)	n	n/N (%)
Visit 1 - Screening	LE gel, 0.5%	206	0	0	0	0	198	96	8	4
	Vehicle	201	1	0	0	0	195	97	5	2
Visit 3 - Post-op Day 1	LE gel, 0.5%	206	0	0	0	0	102	50	104	50
	Vehicle	201	0	0	0	0	100	50	101	50
Visit 4 - Post-op Day 3	LE gel, 0.5%	206	0	0	0	0	139	67	67	33
	Vehicle	201	0	0	1	0	93	46	107	53
Visit 5 - Post-op Day 8	LE gel, 0.5%	206	2	1	6	3	156	76	42	20
	Vehicle	201	2	1	47	23	92	46	60	30
Visit 6 - Post-op Day 15	LE gel, 0.5%	206	4	2	22	11	160	78	20	10
	Vehicle	201	0	0	85	42	89	44	27	13
Visit 7 - Post-op Day 18	LE gel, 0.5%	206	2	1	41	20	151	73	12	6
	Vehicle	201	2	1	112	56	79	39	8	4

5.5 Applicant's Results on Age Subgroups

Section 4.1 shows the treatment effect for different age categories, with categories determined by reviewer based on the quantiles in the population. The following tables, produced by Applicant, show the treatment effect for different age categories, with categories determined by Applicant as less than 65, 65 to75, more than 75.

The Applicant's finding for the Age subgroups is similar to the reviewer's findings. That is, the treatment effect for older subjects is smaller than for younger subjects. More specifically, the Applicant states in Subsection 2.7.3.3.3 of the clinical summary of efficacy that

"In the most elderly age group, LE Gel was superior to vehicle in the complete resolution of pain at postoperative Day 8 ($p < 0.001$), and trended towards superiority in the complete resolution of anterior chamber cells (28.9% vs 19.5% in LE Gel and vehicle groups, respectively, $p = 0.087$) but was not significantly better. This result in the most elderly age group was confirmed by age group analyses of the individual studies. It is also notable that mean efficacy vs vehicle as compared at postoperative Day 8 decreased with increasing age category in this three group integrated analysis (23.4% vs 15.1% vs 9.4% in the ascending age categories). This trend could somewhat be attributable to a higher cell resolution rate in subjects less than 65 years for the LE Gel group (35.3% vs 29.0% vs 28.9% in the ascending age categories) but there is a more important increase

in the proportion of cell resolution in the vehicle group in subjects = 75 years (11.9% vs 13.9% vs 19.5% in the ascending age categories). "

We see in Table 16 to Table 21 the Applicant's results for each study and age category.

Table 16: Primary Efficacy Analysis by Study and Age, Age < 65 subgroup, Study 576

(Source: Applicant's Table 2.2.1.2 in Integrated Summary of Efficacy)

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	LE GEL (N=56)	Vehicle (N=59)	Difference (95% CI)[2]/ p-Value[3]
Complete resolution of anterior chamber cells at Post-op Day 8 (Visit 5)[1]			
Yes	20 (35.7%)	9 (15.3%)	20.5%
No	36 (64.3%)	50 (84.7%)	(3.2%,37.7%)
Subjects without Rescue Medication Use	32	32	0.012/0.026
Subjects with Rescue Medication Use	3	18	
Subjects with Missing Data	1	0	
Grade 0 pain at Post-op Day 8 (Visit 5)[1]			
Yes	44 (78.6%)	26 (44.1%)	34.5%
No	12 (21.4%)	33 (55.9%)	(16.2%,52.9%)
Subjects without Rescue Medication Use	8	15	<0.001/<0.001
Subjects with Rescue Medication Use	3	18	
Subjects with Missing Data	1	0	

[1]Subjects that had missing data or took rescue medication prior to visit 5 are imputed as 'No'.
[2]Difference in percentages; 95% CI based on asymptotic normal approximations.
[3]p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel controlling for site. The Pearson value is the primary outcome and Grade 0 pain only tested if complete resolution of anterior chamber cells is significant at 0.05 level for the Pearson Chi-squared.

Table 17: Primary Efficacy Analysis by Study and Age, Age>=65 to <75, Study 576

(Source: Applicant's Table 2.2.1.2 in Integrated Summary of Efficacy)

	LE GEL (N=83)	Vehicle (N=84)	Difference (95% CI)[2]/ p-Value[3]
Complete resolution of anterior chamber cells at Post-op Day 8 (Visit 5)[1]			
Yes	25 (30.1%)	12 (14.3%)	15.8%
No	58 (69.9%)	72 (85.7%)	(2.3%,29.4%)
Subjects without Rescue Medication Use	52	41	0.014/0.036
Subjects with Rescue Medication Use	6	31	
Subjects with Missing Data	0	0	
Grade 0 pain at Post-op Day 8 (Visit 5)[1]			
Yes	61 (73.5%)	32 (38.1%)	35.4%
No	22 (26.5%)	52 (61.9%)	(20.1%,50.7%)
Subjects without Rescue Medication Use	16	21	<0.001/<0.001
Subjects with Rescue Medication Use	6	31	
Subjects with Missing Data	0	0	

[1]Subjects that had missing data or took rescue medication prior to visit 5 are imputed as 'No'.
[2]Difference in percentages; 95% CI based on asymptotic normal approximations.
[3]p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel controlling for site. The Pearson value is the primary outcome and Grade 0 pain only tested if complete resolution of anterior chamber cells is significant at 0.05 level for the Pearson Chi-squared.

Table 18: Primary Efficacy Analysis by Study and Age, Age>=75, Study 576

(Source: Applicant's Table 2.2.1.2 in Integrated Summary of Efficacy)

	LE GEL (N=64)	Vehicle (N=60)	Difference (95% CI)[2]/ p-Value[3]
Complete resolution of anterior chamber cells at Post-op Day 8 (Visit 5)[1]			
Yes	17 (26.6%)	12 (20.0%)	6.6%
No	47 (73.4%)	48 (80.0%)	(-9.9%,23.0%)
Subjects without Rescue Medication Use	38	27	0.388/0.320
Subjects with Rescue Medication Use	8	21	
Subjects with Missing Data	1	0	
Grade 0 pain at Post-op Day 8 (Visit 5)[1]			
Yes	43 (67.2%)	27 (45.0%)	22.2%
No	21 (32.8%)	33 (55.0%)	(3.5%,40.9%)
Subjects without Rescue Medication Use	12	12	0.013/0.048
Subjects with Rescue Medication Use	8	21	
Subjects with Missing Data	1	0	

[1]Subjects that had missing data or took rescue medication prior to visit 5 are imputed as 'No'.
[2]Difference in percentages; 95% CI based on asymptotic normal approximations.
[3]p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel controlling for site. The Pearson value is the primary outcome and Grade 0 pain only tested if complete resolution of anterior chamber cells is significant at 0.05 level for the Pearson Chi-squared.

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Table 19: Primary Efficacy Analysis by Study and Age, Age <65, Study 577

(Source: Applicant's Table 2.2.1.2 in Integrated Summary of Efficacy)

	LE GEL (N=63)	Vehicle (N=59)	Difference (95% CI)[2]/ p-Value[3]
Complete resolution of anterior chamber cells at Post-op Day 8 (Visit 5)[1]			
Yes	22 (34.9%)	5 (8.5%)	26.4%
No	41 (65.1%)	54 (91.5%)	(11.1%,41.8%)
Subjects without Rescue Medication Use	39	40	<0.001/<0.001
Subjects with Rescue Medication Use	2	13	
Subjects with Missing Data	0	1	
Grade 0 pain at Post-op Day 8 (Visit 5)[1]			
Yes	50 (79.4%)	29 (49.2%)	30.2%
No	13 (20.6%)	30 (50.8%)	(12.4%,48.1%)
Subjects without Rescue Medication Use	11	16	<0.001/0.001
Subjects with Rescue Medication Use	2	13	
Subjects with Missing Data	0	1	

[1]Subjects that had missing data or took rescue medication prior to visit 5 are imputed as 'No'.
[2]Difference in percentages; 95% CI based on asymptotic normal approximations.
[3]p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel controlling for site. The Pearson value is the primary outcome and Grade 0 pain only tested if complete resolution of anterior chamber cells is significant at 0.05 level for the Pearson Chi-squared.

Table 20: Primary Efficacy Analysis by Study and Age, Age>=65 to <75, Study 577

(Source: Applicant's Table 2.2.1.2 in Integrated Summary of Efficacy)

	LE GEL (N=93)	Vehicle (N=74)	Difference (95% CI)[2]/ p-Value[3]
Complete resolution of anterior chamber cells at Post-op Day 8 (Visit 5)[1]			
Yes	26 (28.0%)	10 (13.5%)	14.4%
No	67 (72.0%)	64 (86.5%)	(1.2%,27.7%)
Subjects without Rescue Medication Use	62	45	0.024/0.015
Subjects with Rescue Medication Use	3	18	
Subjects with Missing Data	2	1	
Grade 0 pain at Post-op Day 8 (Visit 5)[1]			
Yes	66 (71.0%)	31 (41.9%)	29.1%
No	27 (29.0%)	43 (58.1%)	(13.3%,44.8%)
Subjects without Rescue Medication Use	22	24	<0.001/<0.001
Subjects with Rescue Medication Use	3	18	
Subjects with Missing Data	2	1	

[1]Subjects that had missing data or took rescue medication prior to visit 5 are imputed as 'No'.
[2]Difference in percentages; 95% CI based on asymptotic normal approximations.
[3]p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel controlling for site. The Pearson value is the primary outcome and Grade 0 pain only tested if complete resolution of anterior chamber cells is significant at 0.05 level for the Pearson Chi-squared.

Table 21: Primary Efficacy Analysis by Study and Age, Age >=75, Study 577

(Source: Applicant's Table 2.2.1.2 in Integrated Summary of Efficacy)

	LE GEL (N=50)	Vehicle (N=68)	Difference (95% CI)[2]/ p-Value[3]
Complete resolution of anterior chamber cells at Post-op Day 8 (Visit 5)[1]			
Yes	16 (32.0%)	13 (19.1%)	12.9%
No	34 (68.0%)	55 (80.9%)	(-4.8%,30.6%)
Subjects without Rescue Medication Use	33	39	0.108/0.072
Subjects with Rescue Medication Use	1	16	
Subjects with Missing Data	0	0	
Grade 0 pain at Post-op Day 8 (Visit 5)[1]			
Yes	40 (80.0%)	32 (47.1%)	32.9%
No	10 (20.0%)	36 (52.9%)	(15.0%,50.9%)
Subjects without Rescue Medication Use	9	20	<0.001/0.001
Subjects with Rescue Medication Use	1	16	
Subjects with Missing Data	0	0	

[1]Subjects that had missing data or took rescue medication prior to visit 5 are imputed as 'No'.
[2]Difference in percentages; 95% CI based on asymptotic normal approximations.
[3]p-Values from Pearson chi-squared statistic/Cochran Mantel-Haenszel controlling for site. The Pearson value is the primary outcome and Grade 0 pain only tested if complete resolution of anterior chamber cells is significant at 0.05 level for the Pearson Chi-squared.

5.6 Observed versus Imputed Anterior Chamber Cell Score Over Time

Mean anterior chamber cell score over time was a secondary endpoint in the two studies. Note that anterior chamber cell grade score is an ordinal endpoint, so the group mean is not as easily interpretable as a responder endpoint such as the primary endpoint. In addition, for the many subjects receiving rescue medication, it is unclear how to impute the values to estimate a treatment effect. Table 22 and Figure 7 explore the impact of the LOCF imputation by comparing it to the observed scores.

Table 22 shows the mean anterior chamber cell score over time in each treatment group and each study. This table shows the mean for observed cell score as well as the mean for imputed cell score using LOCF imputation. Figure 7 shows the jittered individual score over time in anterior chamber cells (gray points) as well as the LOCF mean (solid red line) and the observed mean (dashed red line).

Our observations are the following:

1- In all treatment groups and both studies, the observed cell score mean is lower than the imputed cell score mean indicating that the LOCF imputation is always higher than what is observed. The difference between observed and LOCF means is the highest in the vehicle group, where the mean at Day 18 visit for LOCF imputation is largely driven by observed values at Day 3 visit.

2- LE gel 0.5% has a higher mean cell score than the vehicle, whether for observed values or imputed values. The advantage of LE gel 0.5% over vehicle starts as early as Day 3.

Table 22: Mean Anterior Chamber Cell Score Over Time, Observed and LOCF

	Study 576				Study 577			
Visit	Observed Mean (sd)		LOCF mean (sd)		Observed Mean (sd)		LOCF mean (sd)	
	LE Gel 0.5%	Vehicle	LE Gel 0.5%	Vehicle	LE Gel 0.5%	Vehicle	LE Gel 0.5%	Vehicle
Day 1	2.25 (0.47)	2.28 (0.46)	2.25 (0.47)	2.28 (0.46)	2.32 (0.49)	2.27 (0.46)	2.32 (0.49)	2.27 (0.46)
Day 3	1.53 (0.81)	1.95 (0.94)	1.53 (0.81)	1.96 (0.94)	1.50 (0.70)	1.88 (0.81)	1.50 (0.70)	1.88 (0.81)
Day 8	0.93 (0.83)	1.19 (0.97)	1.05 (0.83)	1.74 (1.14)	0.90 (0.75)	1.33 (0.86)	0.94 (0.79)	1.63 (0.97)
Day 15	0.51 (0.67)	0.70 (0.81)	0.80 (0.67)	1.69 (1.20)	0.43 (0.59)	0.64 (0.73)	0.54 (0.72)	1.33 (1.13)
Day 18	0.43 (0.62)	0.49 (0.66)	0.84 (0.62)	1.67 (1.22)	0.38 (0.58)	0.48 (0.67)	0.54 (0.74)	1.30 (1.15)

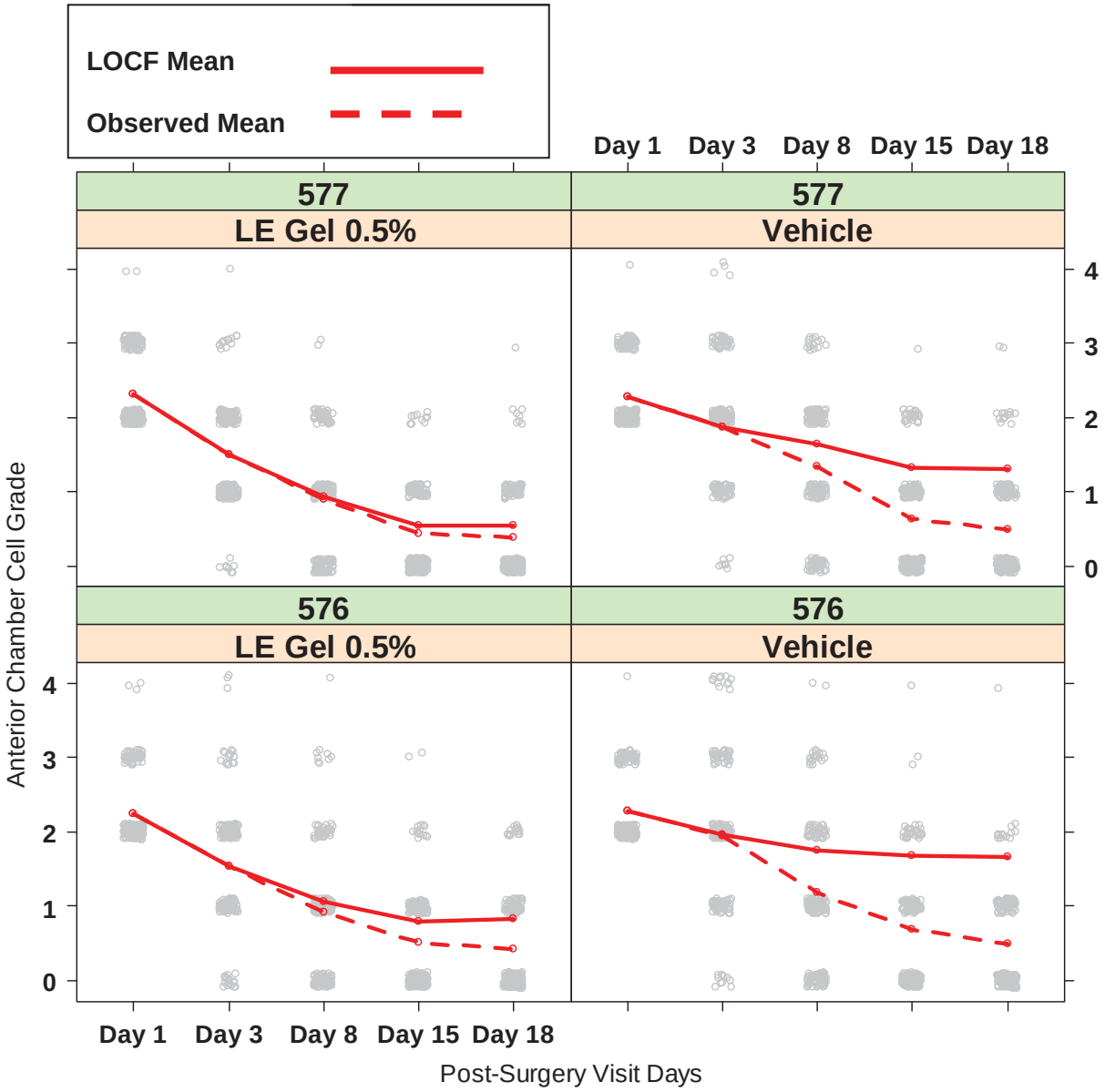

Figure 7: Observed versus Imputed (LOCF) Anterior Chamber Cell Values Over Time

5.7 Anterior Chamber Flare Score versus Anterior Chamber Cell Score Over Time

Anterior Chamber Flare grade score is a secondary endpoint in both studies. It is know to clinicians that the flare score and cell score are associated. The following two figures explore the association between the two scores as well as between the two endpoints of complete resolution of cell and complete resolution of flare. Figure 8 shows the association in the LE gel 0.5% treatment group in each study while Figure 9 shows the association in the vehicle group in each study. The panels in each figure are different visits, the scatter plot in each panel are the jittered observed values for flare score (on the horizontal axis) and cell score (on the vertical axis).

We see that:

1- As expected, there is a positive association between cell score and flare score, but the association is not very strong. The scatter plot in each panel is in the upper quadrant indicating that high cell score generally correspond to high flare score and cell scores tend to be higher than flare score.

2- Almost all subjects with complete resolution of cell has complete resolution of flare, the converse is not true. We see in each panel that when cell score is zero, the flare score is zero for all but a few (2-3 subjects). However, when flare score is zero, cell score can be as high as 3.

3- Although the flare score is in a 5 point scale (0-4), the most common grades given by investigators are 0-2. Grade 3 was rarely given and grade 4 was never given in the two trials.

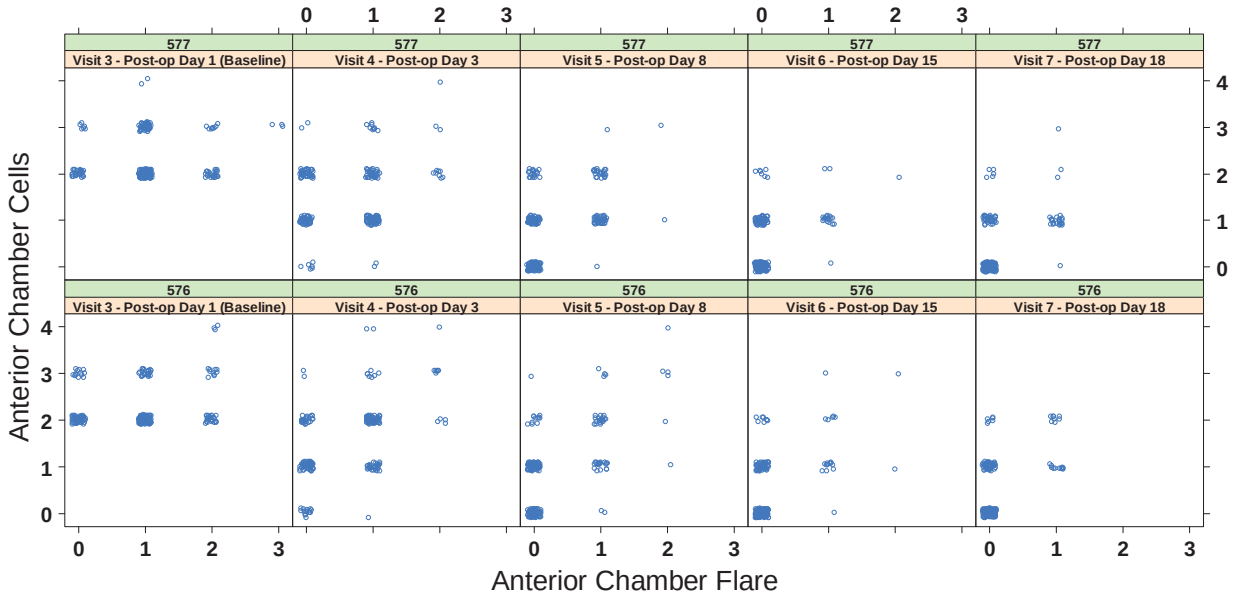

Figure 8: Scatter Plot of Observed Cell Score on Observed Flare Score by visit and study, LE Gel 0.5% Treatment Group

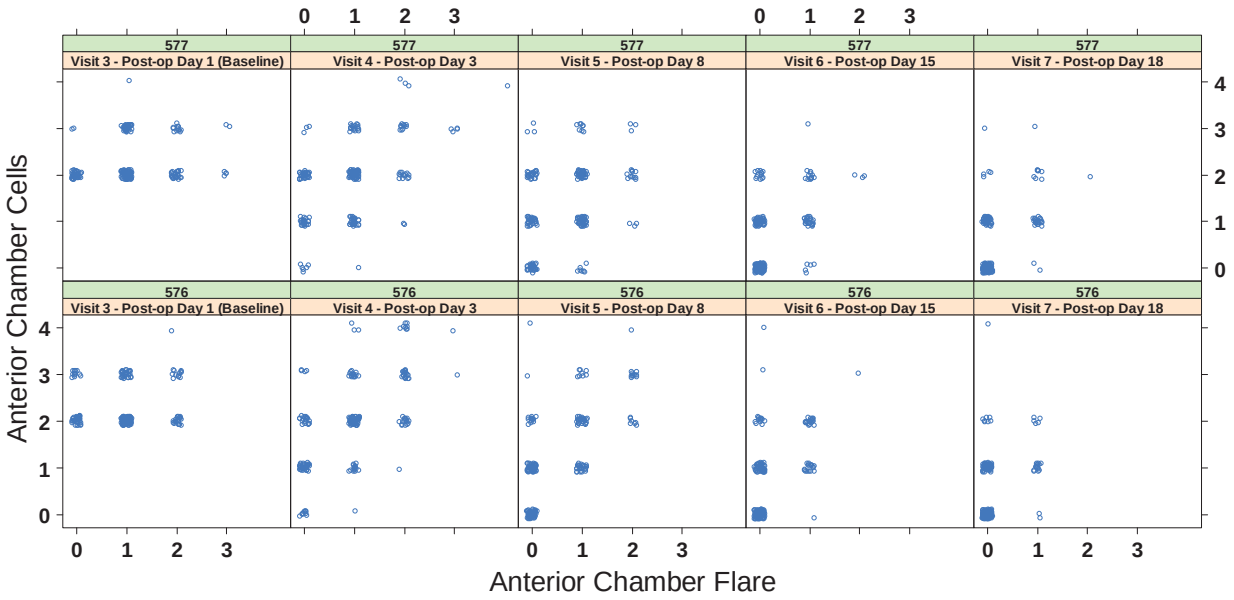

Figure 9: Scatter Plot of Observed Cell Score on Observed Flare Score by visit and study, Vehicle Treatment Group

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/s/

RIMA IZEM
08/23/2012
Table formatting in pdf does not match table formatting in word

YAN WANG
08/23/2012
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202872 **Applicant:** Bausch and Lomb Inc. **Stamp Date:** 11/29/2011

Drug Name: Loteprednol Etabonate Ophthalmic Gel 0.5% **NDA Type:** Standard review

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indication (b) requested.		X		Two pivotal studies support one indication sought. (b) (4) [redacted]
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made.			X	

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

DSMB meeting minutes and data are available.				
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			Little dropout or missing values, treated as failure in primary analysis

Brief summary of controlled clinical trials

The following table is summary of pivotal trials conducted with the gel. The two studies have identical design and similar results

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
576	Randomized, double-masked placebo controlled, parallel arms (14 days post-cataract surgery)	Loteprednol Etabonate gel (203 subjects) Vehicle (203 subjects)	Hierarchical primary endpoints: (1) proportion of subjects with complete resolution of anterior chamber cells (cells=0) at Visit 5 (Postoperative Day 8) , and (2) proportion of subjects with no (Grade 0) pain at Visit 5.	(1) LE Gel, 0.5% (30.5%) vs Vehicle (16.3%), difference 95% CI 14.3% +/- 8.5% (p-value < 0.001) (2) LE Gel 0.5% (72.9%) vs. Vehicle (41.9%), difference 31% +/- 9.6% (pvalue < 0.001)
577	Randomized, double-masked placebo controlled, parallel arms (14 days post-cataract surgery)	Loteprednol Etabonate gel (206 subjects) Vehicle (201 subjects)	Hierarchical primary endpoints: (1) proportion of subjects with complete resolution of anterior chamber cells (cells=0) at Visit 5 (Postoperative Day 8) , and (2) proportion of subjects with no (Grade	(1) LE Gel, 0.5% (31.1%) vs Vehicle (13.9%), difference 95% CI 17.1% +/- 8.5% (p-value < 0.001) (2) LE Gel 0.5% (75.7%) vs. Vehicle (45.8%),

			0) pain at Visit 5.	difference 30% +/- 9.5% (pvalue < 0.001)

Background:

The drug in this application, Loteprednol Etabonate 0.5% gel, is a gel dosage form of a drug product approved in suspension and ointment dosage forms. Loteprednol etabonate 0.5% ophthalmic suspension or Lotemax ® has been approved since 1998 for multiple indications (NDA 20583). The following indications are listed in its label:
" LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment ofthe globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.
…
LOTEMAX is also indicated for the treatment ofpost-operative inflammation following ocular surgery. "

Loteprednol etabonate 0.5% ointment has been approved in 2009 for treatment of inflammation and pain following ocular surgery (NDA 200738).

Sought indication(b) for the gel in this applications are:
- Treatment of Inflammation and Pain following Ocular Surgery, and

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Applicant conducted two clinical trials to support the (b) (4) indication. (b) (4) However, they are using clinical trials conducted for the suspension formulation of this drug as supportive information.

Rima Izem	01-12-2012
Reviewing Statistician	Date
Yan Wang	01-12-2012
Supervisor/Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RIMA IZEM
01/25/2012

YAN WANG
01/25/2012