

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Statistical Review and Evaluation
CLINICAL STUDIES

NDA/Serial Number: 200,738(original)

LE treatment Name: Loteprednol Etabonate Ophthalmic Ointment (LEOO) 0.5%

Indication(s): Treatment of post-operative inflammation and pain following ocular surgery

Applicant: Bausch & Lomb Incorporated

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In this NDA 200738 submission, the applicant [REDACTED] (b) (4)

[REDACTED] The applicant has submitted two phase 3 studies 525 and 526. These two studies have demonstrated that:

- (1) Loteprednol Etabonate Ophthalmic Ointment 0.5% was superior to Vehicle and efficacious in resolution of anterior chamber cells and flare at Postoperative Day 8 (Visit 5);
- (2) Loteprednol Etabonate Ophthalmic Ointment 0.5% was also superior to Vehicle and efficacious in the treatment of pain following cataract surgery at Postoperative Day 8 (Visit 5).

1.2 Brief Overview of Clinical Studies

The applicant submitted two phase-3 studies (525 and 526) in support of the indication of Loteprednol Etabonate (LE) Ophthalmic Ointment 0.5% for the inflammation [REDACTED] (b) (4) [REDACTED] (b) (4). Both phase 3 studies were identical in design. They were randomized, multicenter, double-masked, parallel-group, Vehicle controlled studies.

In both studies, subjects were randomized in a 1:1 ratio to one of the test agents (Vehicle and LE Ophthalmic Ointment 0.5%). Both studies were stratified by site according to a randomization scheme. In study 525, 199 subjects were randomized in the Vehicle group and 201 subjects were randomized for the LE Ophthalmic Ointment 0.5% group. In study 526, 203 subjects were randomized in the Vehicle group and 202 subjects were randomized in the LE Ophthalmic Ointment 0.5% group.

Both studies included 7 visits in a period of approximately 7 weeks: Visit 1 (screening: \leq 14 days prior to surgery), Visit 2 (Surgery), Visit 3 (Postoperative Day 1: 18 to 34 hours post-surgery/randomization), Visit 4 (Day 3 \pm 1: clinical and other assessments), Visit 5 (Day 8 \pm 1: clinical and other assessments), Visit 6 (Day 15 \pm 1: end of treatment) and Visit 7 (Day 18 \pm 1: post-treatment exam). Subjects were instructed to self-administer approximately one-half inch long ribbon of study LE treatment to the lower cul-de-sac of the study eye, four times daily (QID), at approximately 4 hour intervals.

The primary objective of both studies was to compare the safety and efficacy of LE Ophthalmic Ointment 0.5% to Vehicle for the treatment of inflammation and pain following cataract surgery.

The hierarchical primary efficacy endpoints for both studies are:

- The proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8)
- The proportion of subjects with Grade 0 pain at Visit 5 (Postoperative Day 8).

Note: Grade 0 (no) pain was only tested if complete resolution of anterior chamber cells and flare was significant (2-sided p-value ≤ 0.05 , Pearson chi-squared).

1.3 Statistical Issues and Findings

There are no statistical issues identified in this review. The efficacy data submitted for studies 525 and 526 demonstrated that both tests of primary efficacy endpoints were significant in the ITT population at Day 8 (Visit 5):

- LE Ophthalmic Ointment, 0.5% was superior to Vehicle and efficacious in resolution of anterior chamber cells and flare at Postoperative Day 8 when dosed QID for 14 days.
- LE Ophthalmic Ointment, 0.5% was also superior to Vehicle and efficacious in the treatment of pain following cataract surgery at Postoperative Day 8 when dosed QID for 14 days.

Robustness of the Efficacy Results for the Primary Endpoints:

The primary efficacy analysis of the two phase 3 studies was based on the Intent to Treat (ITT) study population, which included all subjects under the treatment to which they were randomized. For these ITT analyses, missing data and data from subjects placed on rescue medication prior to the Postoperative Day 8 visit (Visit 5) were imputed as failures. The applicant conducted sensitivity analysis using the PP population dataset. When the primary analysis was repeated using the PP population, results were similar to that of the ITT Population. This reviewer conducted sensitivity analysis using the ITT population with actual treatment assignments. When the primary analysis was repeated using this alternative population, results were similar to that of the ITT Population.

After the NDA submission, the Agency identified that one of the investigators of study 525, Dr. Kenneth (Sall Research Medical Center), could be problematic in recruiting patients. The Agency requested the applicant to remove all data from the Sall Research Medical Center (Dr. Kenneth Sall) investigator site. Re-analyses of the efficacy dataset, after removing this problematic site, showed the efficacy results were consistent with the primary analyses.

This reviewer conducted Breslow-Day test to investigate the treatments by subgroups (age-group, gender and race) interactions for both studies. The Breslow-Day test did not detect any interactions between the treatment and the subgroups

2 INTRODUCTION

Corticosteroids are potent, non-specific, anti-inflammatory treatments 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. Although corticosteroids are widely used as topical agents for ocular inflammation, most possess a safety risk profile that limits their general utility. The applicant reported that the availability of an ointment formulation of the well-characterized LE ophthalmic suspension, 0.5% would allow physicians a choice of dosage forms in treating ocular inflammation following ocular surgery.

Data sets and all modules containing clinical study reports were submitted electronically. The full electronic path for the study results according to CDER EDR naming convention is as follows:

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The data sets were adequately documented.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Introduction

In this NDA submission, the applicant has submitted data from two Phase 3 studies (525 and 526) for patients treating ocular inflammation following ocular surgery.

Study Designs

Both phase 3 studies (study 525 and study 526) were identical in design. They were randomized, multicenter, double-masked, parallel-group, Vehicle-controlled studies to evaluate the clinical safety and efficacy of LE ophthalmic ointment, 0.5% in comparison to Vehicle for the treatment of inflammation following cataract surgery.

To be eligible for randomization, each subject had to have a sum of anterior chamber cell and flare measures, each on a 0-4 scale, of at least 3 on Postoperative Day 1. The sum of anterior chamber cell and flare measures was also identified as Anterior Chamber Reaction (ACR) in the study protocol. Study 525 was conducted at 20 sites (study period approximately 4 weeks; date of first enrollment: March 14 2008; date of last completion March 23, 2009) in the United States; however, 3 sites did not enroll any subjects. 199 subjects were randomized in the Vehicle group and 201 subjects were randomized in the LE Ophthalmic Ointment 0.5% group. Study 526 was conducted at 19 sites (study period approximately 4 weeks; date of first enrollment: June 20, 2008; date of last completion: May 01, 2009) in the United States, however, 3 sites did not enroll any subjects). 203 subjects were randomized in the Vehicle group and 202 subjects were randomized in the LE Ophthalmic Ointment 0.5% group.

Study duration was approximately 4 weeks from screening to the last Visit (Visit 7). Subjects visited the clinic 7 times. Visit 1 was the Screening visit and occurred 14 days prior to surgery. Visit 2 was the day of surgery. At Visit 3 (Postoperative Day 1), eligibility for randomization into the study was assessed. If eligible, the subject would complete postoperative study Visits 4 through 7:

Visit 4: Day 3 (± 1 day)

- Clinical assessment of ocular symptoms
- Eye examination (VA, IOP, and Biomicroscopy)
- AEs and concomitant medications

Visit 5: Day 8 (± 1 day)

- Clinical assessment of ocular symptoms
- Eye examination (VA, IOP, and Biomicroscopy)
- AEs and concomitant medications

Visit 6: Day 15 (± 1 day) end of treatment

- Clinical assessment of ocular symptoms
- Eye examination (VA, IOP, Biomicroscopy, and Funduscopy)
- AEs and concomitant medications

Visit 7: Day 18 (± 1 day) post-treatment exam

- Clinical assessment of ocular symptoms
- Eye examination (VA, IOP, and Biomicroscopy)
- AEs and concomitant medications
- Exit study

Subjects self-administered an approximately half inch-long (1.3 cm) ribbon of study LE treatment to the lower cul-de-sac of the study eye, four times a day (QID), at approximately four-hour intervals. The initial dose occurred in the clinic, at Visit 3 (Postoperative Day 1). On the day of Visit 3 only, it may not have been necessary for the subject to self-administer all four doses, if time did not permit. Study treatment would

last approximately 14 days, with the last administration being the fourth dose on the day before Visit 6 (Day 15 \pm 1 days).

Primary Efficacy Endpoints:

The hierarchical primary efficacy endpoints for this study are:

1. The proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8)
2. The proportion of subjects with Grade 0 (no) pain at Visit 5 (Postoperative Day 8).

Secondary Efficacy Endpoint:

Secondary endpoints included the proportion of subjects with complete resolution of anterior chamber cells and flare at each visit, the proportion of subjects with Grade 0 pain at each visit, the proportion of subjects with complete resolution of anterior chamber cells at each visit, and the proportion of subjects with complete resolution of anterior chamber flare at each visit. These were considered with and without imputing missing data as failures (subjects placed on rescue medication prior to the visit being summarized would still be considered failures). Additionally, anterior chamber cells and flare composite scores were included as a secondary endpoint.

Safety endpoints:

The safety endpoints for this study are:

- incidence of AEs
- change in IOP
- ocular signs (anterior chamber cells, anterior chamber flare, anterior vitreous haze, bulbar conjunctival injection, chemosis, ciliary flush, corneal edema, eyelid erythema, hyphema, palpebral conjunctival injection, and posterior synechiae)

Inclusion/Exclusion Criteria:

See clinical review for details.

Primary efficacy analyses:

The primary analyses first tested the difference in the proportion of subjects with complete resolution of anterior chamber cells and flare between treatments at Postoperative Day 8 using the Pearson chi-squared statistic. If this test was statistically significant at the two-sided alpha = 0.05 level in favor of LE ophthalmic ointment, then the difference in the proportion of subjects with Grade 0 pain between treatments at the Postoperative Day 8 visit was tested using the Pearson chi-squared statistic at the two-sided alpha = 0.05 level. Further, a 95% confidence interval was constructed around the difference in proportions for each primary outcome at Postoperative Day 8 visit using asymptotic normal approximations.

Hypotheses:

H₀: The difference between subjects treated with LE ointment and subjects treated with Vehicle, in proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) = 0.

H_A: The difference between subjects treated with LE ointment and subjects treated with Vehicle, in proportion of subjects with complete resolution of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) ≠ 0, with superiority claimed if the difference is greater than 0.

H₀₂: The difference between subjects treated with LE ophthalmic ointment and subjects treated with Vehicle, in proportion of subjects with Grade 0 pain at Visit 5 (Postoperative Day 8) = 0.

H_{A2}: The difference between subjects treated with LE ophthalmic ointment and subjects treated with Vehicle, in proportion of subjects with Grade 0 pain at Visit 5 (Postoperative Day 8) ≠ 0, with superiority claimed if the difference is greater than 0.

Secondary Efficacy Analyses

The difference in the proportion of subjects with complete resolution of anterior chamber cells and flare and the difference in the proportion of subjects with Grade 0 pain were independently tested at each visit using the Pearson chi-squared statistic. Further, a 95% confidence interval was constructed around the difference in proportions for each outcome at each visit using asymptotic normal approximations. Additionally, anterior chamber cells and flare were analyzed separately in the same manner described above. Furthermore, Cochran Mantel- Haenszel statistics was calculated on the above, blocking on the site. Change from baseline (Visit 3) in anterior chamber cells and flare composite score (Anterior Chamber Reaction), as well as individual cells and flare scores, were

presented and analyzed using both continuous and discrete statistical methods by treatment and visit, imputing the last observation prior to the rescue medication for visits occurring after rescue medication initiation.

Analysis Populations:

The analysis populations are described in sections below:

Intent-to-Treat (ITT): The ITT population included all randomized subjects. Analysis on the ITT population would be used as the primary efficacy analysis and would be performed for all efficacy endpoints, analyzing subjects under the treatment to which they were randomized. For these ITT analyses, missing data and data from subjects placed on rescue medication prior to the Postoperative Day 8 visit (Visit 5) were imputed as failures

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

The Safety study population included all subjects in the ITT population who received at least one dose of study LE treatment. Analyses performed on the Safety population were according to treatments subjects actually received.

Sample Size Determination:

Study 525 and Study 526:

In both studies, approximately 400 subjects/eyes were planned to be randomized (200 subjects/eyes per treatment group) to yield approximately 180 subjects/eyes per treatment group completing the study, assuming a discontinuation rate of 10%. One-hundred eighty subjects per treatment group yielded 99% power to detect a difference in the proportion of subjects with complete resolution of anterior chamber cells and flare at the Postoperative Day 8 visit between the LE ophthalmic ointment and Vehicle, assuming a resolution rate of 0.365 and 0.146 for the LE ophthalmic ointment and Vehicle, respectively.

Patient Disposition/Study populations/Demographic and Baseline Characteristics at Entry:

Study 525:

Patient Disposition/Study populations:

The summary of the study population is presented in Table 1.

Table 1: Study 525:Patient Disposition

| | LE Ointment (N) | Vehicle (N) | Total (N) |
|----------------------|------------------------|--------------------|------------------|
| Randomized | 201 | 199 | 400 |
| Included In The ITT: | 201 | 199 | 400 |
| Completed | 200 | 193 | 393 |
| Discontinued | 1 | 6 | 7 |
| PP Population | 171 | 170 | 341 |

Data Source: Applicant's Clinical Study Report.

It can be seen from the table above that a total 7 subjects (6 in the Vehicle group and 1 in the LE treatment group) discontinued over the course of the study. The per-protocol (PP) population, defined prior to database lock as subjects who completed the study without any major protocol violation, contained 341 subjects (171 in the LE treatment group and 170 in Vehicle group).

Demographic characteristics:

Baseline demographics for the intent-to-treat (ITT) population for Study 525 are presented in the following table:

Table 2: Study 525 : Demographics (ITT Population)

| Parameter | LE treatment | Vehicle | Total |
|------------------|---------------------|----------------|--------------|
| Gender | | | |
| Male | 83(41.3%) | 89(40.2%) | 163(40.8%) |
| Female | 118(58.7%) | 119(59.8%) | 237(59.3%) |
| Age | | | |
| Mean | 69.2(9.39) | 69.2(8.77) | 69.2 (9.08) |
| Median | 70.0 | 69 | 70 |
| Race | | | |
| White | 183(91.0%) | 179 (89.9%) | 362(90.5%) |
| Non-white | 21(9%) | 24(10.1%) | 45(9.5%) |

Data Source: Applicant’s Clinical Study Report.

It can be seen from Table 2 that demographic characteristics in the ITT population were generally similar between the treatment groups.

Study 526:

The summary of the study population is presented in Table 1.

Table 3: Study 526: Patient Disposition

| | LE Ointment N | Vehicle N | Total N |
|----------------------|--------------------------|----------------------|--------------------|
| Randomized | 203 | 202 | 405 |
| Included In The ITT: | 203 | 202 | 405 |
| Completed | 200 | 200 | 400 |
| Discontinued | 3 | 2 | |
| PP Population | 180 | 173 | 353 |

Data Source: Applicant’s Clinical Study Report.

It can be seen from Table 3 that a total 5 subjects (3 in the Vehicle group and 2 in the LE treatment group) were discontinued over the course of the study. The per-protocol (PP) population, defined prior to database lock as subjects who completed the study without any major protocol violation, contained 353 subjects (180 in the LE treatment group and 173 in Vehicle group).

Baseline demographics for the intent-to-treat (ITT) population for Study 526 are presented in the following table:

Table 4: Study 526 : Demographics (ITT Population)

| Parameter | LE treatment | Vehicle | Total |
|-----------|--------------|------------|-------------|
| Gender | | | |
| Male | 88(43.3%) | 87(43.1%) | 175(43.2%) |
| Female | 115(56.7%) | 115(56.9%) | 230(56.8%) |
| | | | |
| Age | | | |
| Mean | 68.3(9.13) | 69.2(9.36) | 68.8 (9.24) |
| Median | 69.0 | 70 | 70 |
| Race | | | |
| White | 182(89.7%) | 178(88.1%) | 360(88.9%) |
| Non-white | 21(11.3%) | 24(12.9%) | 45(11.1%) |

Data Source: Applicant's Clinical Study Report.

It can be seen from Table 4 that demographic characteristics in the ITT population were generally similar between treatment groups.

Efficacy Results:

Studies 525 and 526 were conducted primarily to assess the efficacy of the LE Ointment against postoperative inflammation. If the treatment was successful against inflammation, then efficacy for relief of postoperative ocular pain was also tested. Therefore, the primary endpoints were hierarchical. This reviewer has verified and reproduced the efficacy results submitted by the applicant.

The efficacy results for the primary endpoints of

- Complete resolution of anterior chamber cells and flare Grade 0 (no) pain at Visit 5 (Postoperative Day 8)

- Grade 0 (no) pain at Visit 5 (Postoperative Day 8)

are summarized below:

Table 5: Primary Efficacy Analysis (Rates between LE Treatment and Vehicle) (ITT Population)

| Endpoint | Protocol 525 (N=400) | | Protocol 526 (N=405) | |
|--|--|------------------------|--|-------------------------|
| | LE treatment vs. Vehicle(p-value) | Difference (95% CI) | LE treatment vs. Vehicle (p-value) | Difference (95% CI) |
| Complete resolutions of anterior chamber cells and flare at Visit5 (Postoperative Day 8) | 48/201(23.9%) vs. 27/199 (13.6%) (p-value: 0.0082) | 10.3% (2.2%, 18.4%) | 64/ 203(31.5%) vs. 23/202(11.4%) (p-value:<0.0001) | 20.1% (11.9%, 28.4%) |
| Grade 0 pain at Visit 5 (Postoperative Day 8) | 156/201 (77.6%) vs. 90/199 (45.2%) (p-value: <0.0001) | 32.4% (22.9%,41.9%) | 149/203 (73.4%) vs. 83/ 202 (41.1%) (p-value : <0.0001) | 32.3% (22.7%, 41.9%) |

Data Source: Applicant’s Clinical Study Report.

Study 525:

In the primary efficacy analysis, the proportion of patients with complete resolutions of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) was 48/201(23.9%) in the Loteprednol group and 23/199 (13.6%) in the Vehicle group [see Table 5]. The difference in proportion was statistically significantly higher with Loteprednol compared to the Vehicle (p-value 0.0082). Following the gate-keeping procedure, the proportion of patients with Grade 0 pain at Visit 5 (p-value <0.0001) was significantly higher with Loteprednol in comparison with the Vehicle (156/201 (77.6%) vs. 90/199 (45.2%)).

Study 526:

In the primary efficacy analysis, the proportion of patients with complete resolutions of anterior chamber cells and flare at Visit 5 was 64/ 203(31.5%) in Loteprednol group and 23/202(11.4%) in Vehicle group [see Table 5]. The difference in proportion was statistically significantly higher with Loteprednol compared to Vehicle(p-value<0.0001). Following the gate-keeping procedure, the proportion of patients with Grade 0 pain at Visit 5 was significantly (p-value <0.0001) higher with Loteprednol compared to Vehicle (149/203 (73.4%) vs. 83/ 202 (41.1%).

Sensitivity analyses:

Per the statistical analysis plan, all of the efficacy analyses that were summarized in the ITT population analyzed subjects under the treatment to which they were randomized (Planned Treatment). This reviewer has conducted the primary analyses using the actual treatment allocation. The analyses are summarized in the following table.

Table 6(reviewer’s): Primary Efficacy Analysis : Rates Between LE Treatment and Vehicle for the ITT Population

| Endpoint | Protocol 525 (N=400) | | Protocol 526 (N=405) | |
|---|---|-----------------------|--|-------------------------|
| | LE treatment vs. Vehicle(p-value) | Difference (95% CI) | LE treatment vs. Vehicle(p-value) | Difference (95% CI) |
| Complete resolutions of anterior chamber cells and flare at Visit 5 (Postoperative Day 8) | 49/201(24.38 %) vs. 26/199 (13.07) (p-value: 0.0038) | 11.31% (3.75%,18.87%) | 66 / 203(32.35 %) vs. 21/202(10.45 %) (p-value:<0.0001) | 22.11% (14.42% ,29.81%) |
| Grade 0 pain at Visit 5 (Postoperative Day 8) | 157/201 (78.11%) vs. 89/199 (44.72 %) (p-value : <0.0001) | 33.33% (24.42%,42.3%) | 151/203 (74.02%) vs. 81/ 202 (40.30%) (p-value :<0.0001) | 34.28% (25.24%,43.33%,) |

The sensitivity analyses based on ITT population with actual treatment assignments were consistent with those of the primary analyses.

After the NDA submission, the Agency identified that one of the investigators of study 525, Dr. Kenneth Sall (Sall Research Medical Center), could be problematic in recruiting patients. The Agency requested the applicant to the remove all data from the Sall Research Medical Center (Dr. Kenneth Sall) investigator site. Re-analyses of the efficacy

dataset, after removing this problematic site, showed the efficacy results were consistent with the primary analyses. These re-analyses are summarized in the following table:

Table 7: Primary Efficacy Analysis (Rates Between LE Treatment and Vehicle) for the ITT Population (without Dr. Sall’s site)

| Endpoint | Protocol 525 (without Dr. Sall’ site) | |
|---|---|--------------------------|
| | LE treatment vs. Vehicle(p-value) | Difference (95% CI) |
| Complete resolutions of anterior chamber cells and flare at Visit 5 | 46/183(25.1%) vs. 27/181(14.9%) (p-value: 0.0149) | 10.2% (1.5%, 18.9%) |
| Grade 0 pain at Visit 5 | 139/183 (76.0%) vs. 74/181(40.9%) (p-value: <0.0001) | 35.1% (25.1%, 41.51%) |

Data Source: Applicant’s NDA submission.

It can be seen that for study 525, the sensitivity analyses based on ITT population after removal of Dr. Sall’s site were consistent with those of the primary analyses.

Per Protocol Analysis:

For both studies, when the primary analyses were repeated using the PP populations, the efficacy results were similar to that of the ITT Population. The efficacy results are summarized in the following table:

Table 8: Efficacy Analysis (Rates Between LE Treatment and Vehicle) (PP Population)

| Endpoint | Protocol 525 (N=341) | | Protocol 526 (N=353) | |
|--|---|------------------------|--|-------------------------|
| | LE treatment vs. Vehicle(p-value) | Difference (95% CI) | LE treatment vs. Vehicle(p-value) | Difference (95% CI) |
| Complete resolutions of anterior chamber cells and flare at Visit5(<i>Postoperative Day 8</i>) | 42/171(24.6%) vs. 22/170 (12.9%) (p-value: 0.0060) | 11.6% (2.8%, 20.4%) | 58/180(32.2%) vs. 19/173(11.0%) (p-value:<0.0001) | 21.2% (12.4%, 30.1%) |
| Grade 0 pain at Visit 5 (<i>Postoperative Day 8</i>) | 133/171 (77.8%) vs. 79/170 (46.5%) (p-value:<0.0001) | 31.3% (21.0%,41.6%) | 133/180 (73.9%) vs. 71/ 173 (41.0%) (p-value:<0.0001) | 32.8% (22.5%, 43.2%) |

Data Source: Applicant’s Clinical Study Report.

Analysis of Secondary Endpoints:

Analyses of important secondary endpoints are described below.

Complete resolutions of anterior chamber cells and flare at Visit 4, Visit 6 and Visit 7:

Secondary efficacy analyses of complete resolutions of anterior chamber cells and flare at Visit 4, Visit 6 and Visit 7 are summarized in the following table:

Table 9: Secondary Efficacy Analysis (Rates Between LE Treatment and Vehicle) of Complete resolutions of Anterior Chamber Cells and Flare by Visit for the ITT Population

| Visit | Protocol 525 (N=400) | | Protocol 526 (N=405) | |
|--|--|--------------------------|--|--------------------------|
| | LE treatment vs. Vehicle (p-value) | Difference (95% CI) | LE treatment vs. Vehicle (p-value) | Difference (95% CI) |
| Visit 4 :Day 3 (±1) | 10/201(5%) vs. 9/199 (4.5%) (p-value:0.83) | 0.5 % (-4.2%, 5.1%) | 10/203(4.9%) vs. 9/202(4.5%) (p-value: 0.83) | 0.5% (-4.1%, 5.1%) |
| Visit 6: Day 15 (±1) | 84/201(41.8%) vs. 30/199(15.1%) (p-value: < 0.0001) | 26.7 % (17.8%, 35.7%) | 107/203(52.7%) vs. 42/202(%) (p-value:<0.0001) | 31.9 % (22.6%, 41.3%) |
| Visit 7:Day 18 (±1) Post-treatment Exam | 86/201(42.8%) vs. 39/199 (%) (p-value: <0.0001) | 23.2% (13.9%, 32.5%) | 100/ 203(49.3%) vs. 46/202(22.8%) (p-value:<0.0001) | 26.5% (17.0%, 36.0%) |

Data Source: Applicant's Clinical Study Report.

It can be seen from the above table that in both studies, the difference between treatment groups at Visit 6 and Visit 7 was significant in favor of LE treatment. However, the difference between treatment groups at Visit 3 was not significant although there is a slight numerical advantage (0.5%) of LE treatment grove over Vehicle treated group.

Grade 0 pain at Visit 4, Visit 6 and Visit 7 :

In addition to primary efficacy analyses at Visit 5, analyses of Grade 0 (no) pain at Visits 4, 6, and 7 (Postoperative Days 3, 15, and 18) in both studies showed significant

differences, demonstrating no ocular pain in subjects treated with LE Ointment (p-value <0.0001).

Conclusions:

The efficacy data submitted demonstrated that

- *LE ophthalmic ointment, 0.5% was superior to Vehicle and efficacious in resolution of anterior chamber cells and flare at Postoperative Day 8 (Visit 5).*
- *LE ophthalmic ointment, 0.5% was also superior to Vehicle and efficacious in the treatment of pain following cataract surgery at Postoperative Day 8 (Visit5).*

3.2 Evaluation of Safety

This section summarizes safety data for studies 525 and 526. See clinical review for further details.

The analysis of safety included a summary of the percentage of subjects with specific treatment-emergent adverse events (TEAE) by treatment group. Incidence of ocular and systemic adverse events was also tabulated by MedDRA preferred term and System Organ Class by treatment group. The primary safety variable was the incidence of subjects with any adverse event during the entire study. In general, descriptive statistics were used without inferential tests for significance.

Study 525:

There were no deaths during the conduct of the study. Two (1 ocular and 1 non-ocular) serious adverse events (SAEs) were reported prior to randomization, both of which were unrelated to study LE treatment/procedures. Five (2 ocular and 3 non-ocular) treatment-emergent SAEs were reported after randomization. Of the two ocular SAEs, one was possibly related to the study LE treatment and probably related to study procedures, and the other unrelated to study LE treatment but definitely related to study procedures. The three non-ocular treatment-emergent SAEs were unrelated to study LE treatment/procedures.

Study 526:

A total of 132 subjects in the Vehicle group required rescue therapy, versus 62 subjects in the LE Ointment group. There were no deaths during the conduct of the study, but six treatment-emergent SAEs were reported by four subjects. All were non-ocular and all

were judged as not related to the study LE treatment. No SAEs occurred prior to randomization or after study exit. See clinical review for further details.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Examination of Subgroups

The applicant did not conduct the tests for homogeneity of subgroups. This reviewer conducted the Breslow-Day test for homogeneity of odds ratios. In the following, the analyses of subgroups by age, sex, and race are provided. Note that the subgroup analyses have to be interpreted very cautiously since they are not powered to test the treatment difference, and there are issues of testing multiple hypotheses.

Age-group:

The following table summarizes subgroup analysis by age group:

Table 12 (reviewer’s): Primary Efficacy Analysis by Age-group for the ITT Population

| Age-group | Endpoint | Protocol 525(N=400) LE treatment vs. Vehicle (p-value) | Protocol 526(N=405) LE treatment vs. Vehicle(p-value) |
|------------------|---|--|---|
| < 65 | Complete resolutions of anterior chamber cells and flare at Visit 5 | 13/55(23.6%) vs. 5/55/(10.0%) (p-value: 0.06) | 22/ 61(36.1%) vs. 5/55(9.1%) (p-value: 0.0006) |
| | Grade 0 pain at Visit 5 | 45/55(81.8%) vs. 24/50(48.0% ^{%%}) (p-value: 0.0003) | 47/61(77.0%) vs.22/55(40.0%) (p-value:< 0.0001) |
| ≥65 to <75 | Complete resolutions of anterior chamber cells and flare at Visit 5 | 18/ 91(19.8%) vs. 12 /99 (12.1%) (p-value: 0.15) | 27/86 (31.4%) vs. 10/86/(11.6%) (p-value: 0.0016) |
| | Grade 0 pain at Visit 5 | 70/91(76.9%) vs. 42/99(42.4%) (p-value:<0.0001) | 64/86(74.4%) vs. 34/86(39.5%) (p-value: <0.0001) |
| ≥75 | Complete resolutions of anterior chamber cells and flare at Visit 5 | 17/55 (30.9%) vs. 10/ 50(20.0%) (p-value: 0.20) | 15/ 56 (26.8%) vs. 8/ 61(13.1%) (p-value: 0.06) |
| | Grade 0 pain at Visit 5 | 41/55(74.5%) vs. 24/50(48%) (p-value:0.005) | 38/56(67.9%) vs. 27/61(44.3%) (p-value:0.01) |

It can be seen from the above table that for both studies the subgroup analysis results are consistent with the primary efficacy analyses.

Gender:

The following table summarizes subgroup analysis by gender:

Table 13(reviewer’s): Primary Efficacy Analysis by Gender for the ITT Population

| Gender | Endpoint | Protocol 525(N=400) LE treatment vs. Vehicle (p-value) | Protocol 526(N=405) LE treatment vs. Vehicle (p-value) |
|--------|---|---|---|
| Male | Complete resolutions of anterior chamber cells and flare at Visit 5 | 21/83(25.3%) vs. 13/80 (16.3%) (p-value:0.1551) | 33/88 (37.5%) vs. 14/87(16.1%) (p-value: 0.0014) |
| | Grade 0 pain at. Visit 5 | 64/ 83(77.1%) vs. 38/ 80(47.5%) (p-value : <0.0001) | 69/88 (78.4%) vs. 36/87(41.4%) (p-value: <0.0001) |
| Female | Complete resolutions of chamber cells and flare at Visit 5 | 27/ 118(22.9%) vs.14/ 119(11.8%) (p-value : 0.0237) | 31/ 115 (27.0%) vs. 9/ 115 (7.8%) (p-value : 0.0001) |
| | Grade 0 pain at Visit 5 | 92/ 118(78.0%) vs.52/ 119(43.7%) (p-value : <0.0001) | 80/115 (69.6%) vs. 47/115(40.9%) (p-value:<0.0001) |

It can be seen from the above table that for both studies the subgroup analysis results are consistent with the primary efficacy analyses.

Race:

The following table summarizes subgroup analysis by race:

Table 14(reviewer’s): Primary Efficacy Analysis by Race for the ITT Population

| Race | Endpoint | Protocol 525(N=400) LE treatment vs. Vehicle (p-value) | Protocol 526(N=405) LE treatment vs. Vehicle (p-value) |
|-----------|---|---|--|
| White | Complete resolutions of anterior chamber cells and flare at Visit 5 | 41/ 183(22.4%) vs. 21/ 179(11.7%) (p-value : 0.0070) | 60/182(33.0%) vs.21/178 (11.8%) (p-value: <0.0001) |
| | Grade 0 pain at. Visit 5 | 145/183 (79.2%) vs. 84/179(46.9%) (p-value: <0.0001) | 132/ 182(72.5%) vs. 75/178(42.1%) (p-value: <0.0001) |
| Non-white | Complete resolutions anterior chamber cells and flare at Visit 5 | 7/18/(38.9%) vs. 6/ 20 (30.0%) (p-value : 0.56) | 4/21 (19.0%) vs. 2/ 24(8.3%) (p-value : 0.29) |
| | Grade 0 pain at. Visit 5 | 11/ 18(61.1%) vs. 6/20(30%) (p-value:0.05) | 17/ 21(81.0%) vs. 8/24 (33.3%) (p-value : 0.001) |

It can be seen from the above table that for both studies the subgroup analysis results are consistent with the primary efficacy analyses.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In studies 525 and 526, both tests of primary efficacy endpoints proved successful in the ITT population at Visit 5 (Day 8), while considering subjects with missing values and subjects requiring rescue medication as treatment failures:

- LE Ophthalmic Ointment, 0.5% was superior to Vehicle and efficacious in resolution of anterior chamber cells and flare at Postoperative Day 8.
- LE Ophthalmic Ointment, 0.5% was also superior to Vehicle and efficacious in the treatment of pain following cataract surgery at Postoperative Day 8.

Robustness of the Efficacy Results for the Primary Endpoints:

The primary efficacy analysis in the two phase 3 studies was based on the Intent to Treat (ITT) study population which included all subjects under the treatment to which they were randomized. For these ITT analyses, missing data and data from subjects placed on rescue medication prior to the Postoperative Day 8 visit were imputed as failures. This reviewer conducted sensitivity analyses using alternative population analysis sets (the PP population and the ITT population with actual treatment assignments). When the primary analyses were repeated using the PP population, results were similar to that of the ITT Population. The sensitivity analyses based on ITT population with actual treatment assignments were consistent with those of the primary analyses.

After the NDA submission, the Agency identified that one of the investigators of study 525, Dr. Kenneth Sall (Sall Research Medical Center),could be problematic in recruiting patients. The Agency requested the applicant to the remove all data from the Sall Research Medical Center (Dr. Kenneth Sall) investigator site. Re-analyses of the efficacy dataset, after removing this problematic site, showed the efficacy results were consistent with the primary analyses.

This reviewer conducted Breslow-Day test to investigate the treatments by subgroups (age-group, gender and race) interactions for both studies. The Breslow-Day test did not detect any interactions between the treatment and the subgroups.

5.2 Conclusions and Recommendations

The efficacy data submitted for studies 525 and 526 demonstrated that:

(1) LE Ophthalmic Ointment 0.5% was superior to Vehicle and efficacious in resolution of anterior chamber cells and flare at Postoperative Day 8 (Visit 5) when dosed QID for 14 days;

(2) LE Ophthalmic Ointment 0.5% was also superior to Vehicle and efficacious in the treatment of pain following cataract surgery at Postoperative Day 8 (Visit 5) when dosed QID for 14 days.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|---------------------|--------------------------------------|
| NDA-200738 | ORIG-1 | BAUSCH AND LOMB INC | LOTEPREDNOL ETABONATE OINTMENT, 0.5% |

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/s/

MUSHFIQUR M RASHID
08/19/2010

YAN WANG
08/19/2010