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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: 21-737

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Indication(s): Non-Infectious Posterior Uveitis

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Table of Contents

Statistical Review and Evaluation	1
1 Executive Summary	4
1.1 Conclusions and Recommendations	4
1.2 Brief Overview of Clinical Studies	4
1.3 statistical issues and findings	5
2 introduction	6
2.1 overview	6
2.2 Data Sources	7
3 Statistical Evaluation	7
3.1 Evaluation of efficacy	7
3.1.1 Study # BLP 415-001 Phase IIb/III	7
3.1.1.1 Design and Objectives	7
3.1.1.2 Primary Efficacy Endpoint	8
3.1.1.3 Secondary Efficacy endpoint	8
3.1.1.4 Patients Analyzed	9
3.1.1.5 Disposition of Patients, Demography	9
3.1.1.6 Sample size determination and Efficacy Analysis	9
3.1.1.7 Sponsor's Results and Conclusions	12
3.1.1.8 Reviewer's Findings and Conclusions	14
3.1.2 Study # 415-004	14
3.1.2.1 Design and Objectives	14
3.1.2.2 Primary Efficacy Endpoint	15
3.1.2.3 Secondary Efficacy endpoint	16
3.1.2.4 Patients Analyzed	16
3.1.2.5 Disposition of Patients, Demography, and Baseline Disease Conditions	16
3.1.2.6 Sample size determination and efficacy analysis	17
3.1.2.7 Sponsor's Results and Conclusions	20
3.1.2.8 Reviewer's Findings and Conclusions	22

3.2 Evaluation of safety	22
3.2.1 <i>Sponsor's analysis of safety data</i>	22
3.2.1.1 <i>Study #BLP 415-001</i>	22
3.2.1.2 <i>Study #BLP 415-004</i>	23
3.2.2 <i>Reviewer's analysis of safety data</i>	24
4 Findings in spacial/Subgroup Populations	24
4.1 Sponsor's sub-group analysis	24
4.1.1 <i>Study #BLP 415-001</i>	24
4.1.1.1 <i>Sub-group analysis by Age</i>	24
4.1.1.2 <i>Sub-group analysis by Gender</i>	24
4.1.1.3 <i>Sub-group analysis by Race</i>	24
4.1.1.4 <i>Analysis by Other Special/ Subgroup populations</i>	24
4.1.2 <i>Study #BLP 415-004</i>	24
4.1.2.1 <i>Sub-group analysis by Age</i>	24
4.1.2.2 <i>Sub-group analysis by Gender</i>	24
4.1.2.3 <i>Sub-group analysis by Race</i>	25
4.1.2.4 <i>Analysis by Other Special/ Subgroup populations</i>	25
4.2 Reviewer's sub-group analysis	25
5 Summary and conclusions	25
5.1 Statistical issues and collective evidence	25
5.2 Conclusions and recommendations	26
6 Appendix	27

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

In this submission the sponsor included reports of two completed Phase 3 studies, namely Studies # BLP 415-001 and # BLP 415-004 to establish the efficacy of Intravitreal Fluocinolone Acetonide Implant (0.59 or 2.1 mg) by reducing the recurrence of uveitis inflammation in patients with non-infectious uveitis affecting the posterior segment of the eye. The sponsor also included partial information and/or the protocols of four other studies, namely

_____ . These studies are either on-going or extension into compassionate use of the first two completed studies, and therefore not reviewed here. This reviewer's report is based only on data of the two completed studies, namely Studies # BLP 415-001 and # BLP 415-004.

Results from Studies # BLP 415-001 and # BLP 415-004 showed that patients in both 0.59 and 2.1 mg of Fluocinolone Acetonide Implant dose groups had statistically significant reduction in the recurrence of uveitis inflammation in patients with non-infectious uveitis affecting the posterior segment of the eye. However, it should be noted that neither of the two studies had any control group, therefore a comparative statement on efficacy could not be made.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this submission the sponsor included reports from two completed Phase 3 studies, namely Studies # BLP 415-001 and # BLP 415-004. The sponsor also included partial information and/or the protocols of four other studies, namely Studies

_____. Following are the titles and brief descriptions of the six studies:

Study # BLP 415-001 Phase IIb/III: "A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide (0.5 or 2.1 mg) Implant in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye".

This study was completed and a full report was submitted.

Study # BLP 415-004 Phase III: "A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide (0.5 or 2.1 mg) Implant in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye".

This study was completed and a full report was submitted.

Studies #BLP 415-001 and # BLP 415-004 were complete and full reports of efficacy and safety were submitted. For Studies _____ enrolment were not completed, and no decoding has been performed. Only two interim reports of the safety data were submitted. For Studies _____ only the protocols have been submitted. However, so far no patient has been recruited for these two studies.

1.3 STATISTICAL ISSUES AND FINDINGS

In some of the original protocols the doses in the two groups were defined as 0.5 mg and 2 mg. Since then the reference to the 0.5 mg has been changed to the 0.59 mg and 2 mg has been changed to 2.1 mg to accurately reflect the correct label claim. The main statistical issue was to compare the correlated pre and post operation recurrence rates of uveitis inflammation in patients with non-infectious uveitis affecting the posterior segment of the eye.

2 INTRODUCTION

2.1 OVERVIEW

In this NDA submission the sponsor included data to support their claim that the use of Intravitreal Fluocinolone Acetonide Implant (0.59 or 2.1 mg) is effective in patients with non-infectious uveitis affecting the posterior segment of the eye with respect to reducing the recurrence of uveitis inflammation of the study eye from the period of assessment of 34 weeks prior to implantation to the period of assessment of 34 week following implantation (primary efficacy).

The sponsor included reports of two completed Phase 3 studies, namely Studies # BLP 415-001 and # BLP 415-004 to establish the efficacy of Intravitreal Fluocinolone Acetonide (0.59 or 2.1 mg) Implant by reducing the recurrence of uveitis inflammation in patients with non-infectious uveitis Affecting the posterior segment of the eye. The sponsor also included partial information and/or the protocols of four other studies, namely Studies # _____ and _____.

Because Studies # _____ are supplemental this reviewer's report is based only on data of the two completed studies, namely Studies # BLP 415-001 and # BLP 415-004. However, data of Studies # _____

_____ should be analyzed to support the efficacy of the study drug as they become available.

2.2 DATA SOURCES

The submission was in hard copy. Submitted data was stored in folder \\Cdsub1\n21737\N_000\2004-10-07\CRT\datasets in FDA's Electronic Document Room (EDR). The data quality of the submission was within acceptable limit.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY # BLP 415-001 PHASE IIB/III

Title: "A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide (0.5 or 2.1 mg) Implant in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye".

3.1.1.1 Design and Objectives

This is a 3-year multi-center, randomized, double-masked, controlled, safety and efficacy study to evaluate the effect of 0.59 or 2.1 mg fluocinolone acetonide intravitreal implants on the recurrence of inflammation secondary to posterior uveitis in patients with unilateral or bilateral uveitis. The primary efficacy outcome is based on the change in disease status of the study eye from the 34 weeks period of assessment prior to implantation to the 34-week period following implantation.

All patients entering the study were randomly assigned to one of two treatments, 0.59 mg or 2.1 mg fluocinolone acetonide intravitreal implant in the ratio of 2:3 (0.59 mg to 2.1 mg groups). Only one eye (study eye) received an implant. In patients with unilateral disease, the affected eye was the study eye. In patients with bilateral disease the study eye was the more severely affected eye, i.e., the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA or if equal, the eye clinically judged by the treating physician to be the more severely affected eye.

Study objectives were:

- To evaluate the safety and efficacy of intravitreal fluocinolone acetonide implants in the management of patients with non-infectious uveitis affecting the posterior segment of the eye.
- To compare the safety and efficacy of 2 doses of fluocinolone acetonide (0.59 or 2.1 mg) delivered by an intraocular/intravitreal implant in patients with non-infectious uveitis affecting the posterior segment of the eye.

3.1.1.2 Primary Efficacy Endpoint

The primary efficacy outcome was the change in recurrence of uveitis inflammation of the study eye from the period of assessment of 34 weeks prior to implantation to the period of assessment of 34 week following implantation.

- *Recurrence of uveitis Pre-implantation:* A recurrence with onset within 34 weeks prior to implantation is defined by the investigator's assessment that the patient satisfied the definition of a "protocol defined" recurrence as recorded on the Uveitis History CRF. This can be contradicted by a maximum anterior chamber cell score <2, a maximum vitreous haze score <2 and a maximum change in visual acuity <0.3 logMAR or Snellen equivalent.
- *Recurrence of uveitis Post-implantation:* The post-implantation criteria by the 34 week visit were scored on a protocol specified scale and defined as a change from baseline (screening). A post-implantation recurrence by the 34 week visit was defined by a ≥ 2 step increase compared to baseline in the number of cells in the anterior chamber per high power field and not attributable to conditions other than non-infectious posterior uveitis, or an increase in the vitreous haze of ≥ 2 steps compared to baseline not attributable to conditions other than non-infectious posterior uveitis, or a deterioration in visual acuity of at least 0.30 logMAR units from baseline, not attributable to conditions other than non-infectious posterior uveitis, or failure ever to be observed after the 24-week visit.

For any eye not observed after the 24-week visit it was assumed, due to lack of evidence to the contrary, that the eye experienced a recurrence. The determination of post implantation recurrences was based on the visual acuity and slit-lamp examination findings.

To prevent post-operative inflammatory reactions following the original implantation procedure from being reported as uveitis recurrences, assessments for recurrence of uveitis began one week after complete tapering off pre-study anti-inflammatory and/or immunosuppressive medications. When other intercurrent ocular surgical procedures were required, assessments for recurrence resumed one week after discontinuation of postoperative topical anti-inflammatory medications. Post-operative inflammation requiring immunosuppressant or anti-inflammatory therapy for 12 weeks or more were considered a recurrence despite the fact that the original inflammation may have been brought about by the surgical procedure.

3.1.1.3 Secondary Efficacy endpoint

Three types of comparisons were performed in the secondary efficacy outcomes namely, between-patient treatment (doses), within patient fellow eye, and within patient historical.

The secondary end points were:

- Post-implantation recurrence of uveitis rate: within-patient comparison of eyes (implant vs. fellow)
- Time-to-recurrence: within-patient comparison of eyes (implant vs. fellow)
- Within-patient comparison of adjunctive treatment required, pre- versus post implantation
- Visual acuity: within-patient comparison of responding eyes (implant vs. fellow)
- Area of CME: within-patient comparison of responding eyes (implant vs. fellow)
- Post-implantation uveitis rate: between patient treatment group comparison
- Time-to-recurrence: between treatment group comparison
- Quality of life surveys

3.1.1.4 Patients Analyzed

Intent-to-Treat Population: All enrolled patients who were implanted and had at least one post-implant examination were included in the intent-to-treat population (N = 278).

Reviewer's comment: A more conservative definition of ITT population is all enrolled patients who receive treatment. A total of 278 patients were enrolled in this study. All of these enrolled patients had at least one post-implant examination. Therefore, in this study the protocol defined ITT population is the same as from the more conservative definition stated above.

Evaluable Population: An evaluable population was defined by a technical review and other clinical evaluation.

Safety Population: All patients who received study medication comprised the safety population.

3.1.1.5 Disposition of Patients, Demography

Disposition and demographic characteristics of ITT patients is given in Tables 1 and 2, respectively in the appendix. Total of 278 patients were enrolled into this study. Of these, 271 (97.5%) completed 34 weeks of the study. Of the 7 patients not completing three patients discontinued due to adverse events, three were lost to follow-up, and one was a protocol violation.

The population had a mean age of about 44 years, ranging from 7 to 84 years. There were approximately 66% Caucasian and 18% Black. About 72% of the patients were female. Approximately 77% of the population had bilateral disease, and about 68% were using systemic immunomodulatory therapy for control of uveitis prior to enrollment.

There were no statistically significant differences in demographics between the two treatment groups (p-values were between 0.3004 to 0.9932).

3.1.1.6 Sample size determination and Efficacy Analysis

3.1.1.6.1 Determination of sample size

In initial evaluations conducted under INDs _____ seven eyes treated with 2.1 mg implants showed that this dose had a 95% probability of being effective in at least 66% of cases and has a 50% probability of being effective in at least 90% of cases. The efficacy and safety of the 0.59 mg dose was not yet known. If the recurrence rates for the 2.1 mg dose were as shown in Table 3 in the appendix, and the recurrence rates of the 0.59 mg dose were at least as great as the value shown in the same table, then a sample size of 150 for the 2.1 mg group and 100 for the 0.59 mg group (a total of 250 subjects) provides 90% power for comparing the proportions of recurrence rates in the two dose groups using the 2 tail chi-square test with Type 1 error of 0.05.

Reviewer's Comment: It should be noted that in the sample size calculation a between group comparison were performed using the chi-square test, contrary to a comparison of pre versus post recurrences of uveitis within the same group using the McNemar's test specified as primary efficacy analysis. Therefore, for the calculated sample size, it is not clear what the actual power of the test was.

3.1.1.6.2 Primary Efficacy Analysis

The primary efficacy outcome was based on the change in disease status of the study eye from the 34 weeks period of assessment prior to implantation to the 34 week period following implantation. Following the protocol if a patient experienced one or more pre-implantation recurrences, the patient was assigned a positive disease status, otherwise the disease status was negative. A positive post implantation disease status was assigned if the patient suffered at least one recurrence, or if the patient was never observed after the 24-week visit; otherwise it was negative.

The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was primarily based on the combined dose groups. However, results by dose groups were also investigated.

3.1.1.6.3 Handling of dropouts or missing data

For parameters measured on a continuous scale, analyses were performed on the 34-Week Last Observation Carried Forward (LOCF) scores, defined as the last score observed in the study up to and including the 34-Week visit. In the event that the 34-Week visit was missed, then the 34-Week LOCF score was the last value obtained prior to study day 245 (which is 35 weeks post implantation, since it is noted that the end of the protocol-stated window for the 34-Week scheduled visit was 34 ± 1 week). For analyses assessing the occurrence of a condition, an analysis was performed on the 'Overall' time frame, in which the occurrence of the condition is noted if it was present at any post-implantation study visit up to the 34-Week visit. In the event that the 34-Week visit was missed, then the Overall score noted the occurrence of the condition over the entire study up through study day 245. An exception to this imputation strategy was employed for the analysis of posterior uveitis. For any eye not observed after the 24-week visit, it was assumed, due to lack of evidence to the contrary, that the eye experienced a recurrence.

3.1.1.6.4 Secondary Efficacy analysis

Within-patient comparison of post-implantation recurrence of uveitis rate (implant vs. fellow eyes): The proportion of patients whose recurrence status is different between the two eyes was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups. However, results by dose group were also investigated. Two populations were analyzed namely, patients presenting with bilateral uveitis and all patients.

Time-to-recurrence (Within-patient comparison of eyes implant vs. fellow): The distribution of time to first post-implantation recurrence of uveitis was determined for the implant and fellow eyes. Eyes without a recurrence were censored at their last observation. Kaplan-Meier plots were used for a descriptive analysis of this data. This outcome was based on the combined dose groups. However, results by dose groups were also investigated. Two populations were analyzed namely, patients presenting with bilateral uveitis and all patients.

Within-patient comparison of eyes previously controlled with systemic medication, pre- versus post-implantation: If a patient's posterior uveitis was being treated with systemic therapy at the time of enrollment, the patient was assigned a positive status, otherwise the status was negative. A positive post implantation status was assigned if the patient was receiving systemic therapy at the 34 week visit for control of non-infectious posterior uveitis; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups. However, results by dose groups were also investigated.

Within patient comparison of patients receiving peri-ocular injections to control uveitis, pre- versus post-implantation: If a patient received peri-ocular injections for the treatment of posterior uveitis during the 34 weeks prior to enrollment, the patient was assigned a positive status, otherwise the status was negative. A positive post-implantation status was assigned if the patient received peri-ocular injections during the 34 week period after implantation for control of non-infectious posterior uveitis; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups. However, results by dose groups were also investigated.

Within patient comparison of patients receiving topical corticosteroids to control uveitis, pre- versus post-implantation: If a patient received topical ocular corticosteroids for the treatment of posterior uveitis during the 34 weeks prior to enrollment, the patient was assigned a positive status, otherwise the status was negative. A positive post-implantation status was assigned if the patient received topical ocular corticosteroids during the 34 week period after implantation for control of non-infectious posterior uveitis; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups. However, results by dose groups were also investigated.

Visual Acuity (Within-patient Comparison of Responding Eyes implant vs. fellow): A positive response was assigned if the patient experienced at least a 3 line improvement in visual acuity at Week 34, otherwise the response was negative. Patients not observed at Week 34 were assigned a negative response. The proportion of patients whose response status was different between the two eyes was analyzed using McNemar's test for correlated proportions. Descriptive statistics on the observed VA and change from baseline scores, as well as the distribution of change from baseline scores categorized by the number of lines gained and lost were presented. This outcome was based on the combined dose groups. However, results by dose groups were also investigated. Two populations were analyzed: patients presenting with bilateral uveitis and all patients.

Area of CME (Within-patient comparison of responding eyes implant vs. fellow): The change from baseline in area of CME on the 300-second frame of the fluorescein angiogram at 34 weeks post-implantation in the implanted eye was compared to the fellow non-implanted eye in patients with bilateral disease at entry. A positive response was assigned if the measured area of CME on the 300-second frame of the angiogram at Week 34 was less than at baseline, otherwise the response was negative. Only patients observed at baseline and Week 34 were included in this analysis. The proportion of patients whose response status was different between the two eyes was analyzed using McNemar's test for correlated proportions. Descriptive statistics on the observed measured area and change from baseline scores are presented.

This outcome was based on the combined dose groups. However, results by dose groups were also investigated. Two populations were analyzed: patients presenting with bilateral uveitis and all patients.

Post-implantation uveitis rate (Between treatment group comparison): The comparison of the treatment groups with respect to the proportion of patients who experienced a recurrence was performed using the Cochran-Mantel-Haenszel Chi-squared test, stratified for study site and type of prior therapy.

Time-to-recurrence (Between treatment group comparison): The distribution of time to first post-implantation recurrence of uveitis in the implant eye was compared between treatment groups by proportional hazards regression stratified by investigative site and prior therapy. Eyes without a recurrence were censored at their last observation. Kaplan-Meier plots were used for descriptive analysis.

Pre- versus post-implantation occurrence of intraocular inflammation based upon anterior chamber cells or vitreous haze: For the pre-implantation period, if the Uveitis History CRF documented a score ≥ 2 for anterior chamber cells or vitreous haze, the patient was assigned a positive intraocular inflammatory status, otherwise the status was negative. For the post-implantation period, a positive status was assigned if the patient experienced an increase in anterior chamber cells or vitreous haze ≥ 2 or if the patient was never observed after the 24-week visit; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups. However, results by dose groups were also investigated.

Quality of life surveys: The quality-of-life survey was evaluated using the SF-36, VFQ-25, and VFQ-37 scores. The sub-scale and the composite scale data were summarized using descriptive statistics. Continuous variables were analyzed using the paired t-test and categorical variables were analyzed using the Wilcoxon signed-rank test.

3.1.1.7 Sponsor's Results and Conclusions

3.1.1.7.1 Primary efficacy outcome

Pre- versus post-implantation recurrence of uveitis Study eyes: A summary of uveitis recurrence during the 34-week period prior to, and during the 34-week period subsequent to implantation is shown in Table 4 in the appendix. For both doses combined, 51.4% (143/278) had recurrences during the 43 week period prior to implantation, while 6.1% (17/278) presented with recurrences during the period subsequent to implantation ($p < 0.0001$). During the pre-implantation period, a total of 143 recurrences were reported in 278 study eyes, with 22.3% (62/278) of the study eyes reporting more than one recurrence (ranging from 2 to 7). No study eye reported more than one recurrence during the post-implantation period.

Six of the 17 recurrences in study eyes reported above represent patients who were not observed beyond week 24. These patients were 118-2050, 124-2057, 125-2198, 144-2230, 144-1227 and 133-1009.

This primary efficacy outcome measure was also analyzed on the population as randomized ($n=108$ and 170 for 0.59 mg and 2.1 mg, respectively). The results of this analysis paralleled those of the "as treated" analysis.

3.1.1.7.2 Secondary Efficacy outcome

Fellow eyes: A summary of uveitis recurrence in fellow eyes during the 34-week period prior to, and during the 34-week period subsequent to implantation is shown in Table 5 in the appendix. Two fellow eyes, one in each dose group, were prosthetic, and thus the sample size is 276 eyes. For both doses combined 20.3% (56/276) had recurrences during the period prior to implantation, while 42.0% (116/276) presented with recurrences during the period subsequent to implantation ($p < 0.0001$).

Within-patient comparison of post-implantation recurrence of uveitis rate (implant vs. fellow eyes): A summary of uveitis recurrence during the 34-week period prior to, and during the 34-week period subsequent to implantation is shown in Table 6 in the appendix. For both doses combined 6.1% (17/278) of study eyes had recurrences during the period subsequent to implantation, while 42.0% (116/276) of fellow eyes had recurrences during this period ($p < 0.0001$).

Time-to-recurrence (Within-patient comparison of eyes implant vs. fellow): The time-to-recurrence of uveitis for implant vs. fellow eyes was evaluated by Kaplan-Meier methods (freedom from recurrence). Figures 1A and Figure 1B in the appendix show the Kaplan-Meier curves for 0.59 mg and 2.1 mg treatment groups. The plots shows that in both dose groups combined the uveitis recurred in the fellow eyes sooner than implanted eyes. An additional analysis comparing study vs. fellow eyes for the ITT population with bilateral disease was supportive of this analysis.

Visual Acuity (Within-patient Comparison of Responding Eyes implant vs. fellow): The proportion of patients with an improvement in visual acuity in study eyes vs. fellow eyes at week 34 is shown in Table 7 in the appendix. For both doses combined 21.0% (56/267) of study eyes improved by at least 0.30 logMAR, while 6.0% (16/265) of fellow eyes improved by the same criterion ($p < 0.0001$).

Area of CME within-patient comparison of eyes with a decrease in CME 300 sec (implant vs. fellow): Patients underwent fluorescein angiography at screening, week 8 and week 34. This analysis was masked to study subjects and Investigators. The proportion of patients with an improvement in the area of CME at week 34 is shown in Table 8 in the appendix. For both doses combined 71.1% (81/114) of study eyes improved, while 24.6% (28/114) of fellow eyes improved ($p < 0.0001$). An analysis of eyes with bilateral disease at baseline provided similar results.

Post-implantation uveitis rate between treatment group comparison: The recurrence rate by dose group is shown in Table 9 in the appendix. The rate in the 0.59 mg group study eyes was 6.4% (7/110) and that seen in the 2.1 mg group, 6.0% (10/168). The difference was not statistically significant ($p = 0.9770$).

Time-to-recurrence Between treatment group comparison: An analysis of the freedom from recurrence of uveitis between treatments was performed using a proportional hazard model, stratified by site and prior therapy. The hazard ratio between doses was 1.107 (95% C.I., 0.391 – 3.133; $p = 0.8486$).

Pre- versus post-implantation occurrence of intraocular inflammation based upon anterior chamber cells or vitreous haze Study Eye: A summary of intraocular inflammation during the 34-week period prior to, and during the 34-Week period subsequent to implantation (including any post-operative periods) is shown in Table 10 in the appendix. For both doses combined, 53.6% (149/278) had intraocular inflammation during the period prior to implantation, while 55.0% (153/278) presented with intraocular inflammation during the period subsequent to implantation ($p = 0.7371$).

Pre- versus post-implantation occurrence of intraocular inflammation based upon anterior chamber cells or vitreous haze Fellow Eye: A summary of intraocular inflammation during the 34-week period prior to, and during the 34-week period subsequent to implantation (including any post-operative periods) is shown in Table 11 in the appendix. For both doses combined 25.7% (71/276) had intraocular inflammation during the period prior to implantation, while 47.5% (131/276) presented with intraocular inflammation during the period subsequent to implantation ($p < 0.0001$).

Quality of life surveys: At study entry, mean (\pm S.D.) measures for SF-36 (Physical composite), SF-36 (Mental composite), VFQ-25 composite and VFQ-37 composite were 48.0 ± 10.2 , 50.5 ± 10.8 , 66.9 ± 19.4 and 67.8 ± 19.4 , respectively (scale of 0-100). To assess the effect of the implant on change in health-related and vision targeted quality of life, preoperative sub-scale and composite scores of the SF-36, VFQ-25 and VFQ-37 were subtracted from visit 11 (week 34) follow-up scores.

For the SF-36, mean scores were somewhat lower at follow-up indicating decreased health status. The only statistically significant ($p < 0.05$) change in mean score was for the physical health problems sub-scale, where the follow-up mean score was approximately six points lower than the baseline mean score. For the VFQ-25 and VFQ-37, mean changes were in the positive direction (better vision-targeted health status) and statistically significant for most of the sub-scales and for both of the composites. For the VFQ-25 the mean change scores ranged from 5.3 to 13.3 points, with a mean change of 6.0 points for the VFQ-25 composite. The greatest mean change (13.3 points) was found for the sub-scale measuring mental health symptoms due to vision. For the VFQ-37 mean change scores ranged from 4.6 to 12.2 points, with a mean change of 5.6 points for the VFQ-37 composite. Results for the VFQ-37 were very similar to the VFQ-25. The association between treatment dose and QOL scores were not statistically significant.

3.1.1.8 Reviewer's Findings and Conclusions

This reviewer reanalyzed the primary efficacy variable. In the submitted data set "UVHIST" the variable RECURYN represents the presence or absence of protocol defined pre-treatment UV-recurrence. In this reviewer's analyses if RECURYN had a value 'Y' the pre-treatment recurrence was assumed to be positive. Also the submitted data set "UVRECUR" has variables RCODE and ONSETDT. The RCODE has 3 values (1, 2, and 3)¹ representing the severity of UV-recurrence, while the ONSETDT shows the onset dates. In some cases while the onset date was present the severity was not mentioned i.e. RCODE was empty. In this reviewer's analysis if an onset date was present UV-recurrence was assumed to be positive regardless of the information of its severity. Data were analyzed using the McNemars's test on ITT population. Table 12 in the appendix shows this reviewer's analysis. There are some discrepancies between this reviewer's count of number of patients with positive UV-recurrence in both pre and post treatment. However, the general conclusion agreed with those of the sponsor i.e. both doses of Fluocinolone Acetonide showed statistically significantly low post-treatment UV-recurrence compared to pre-treatment UV-recurrence.

3.1.2 STUDY # 415-004

Title: "A Multicenter, Randomized, Double-Masked, Controlled Study to Evaluate the Safety and Efficacy of an Intravitreal Fluocinolone Acetonide (0.5 or 2.1 mg) Implant in Patients with Non-Infectious Uveitis Affecting the Posterior Segment of the Eye".

3.1.2.1 Design and Objectives

This was a 3-year multi-center, randomized, double-masked, controlled, safety and efficacy study in patients with unilateral or bilateral uveitis to evaluate the effect of fluocinolone acetonide intravitreal implants on the recurrence of inflammation secondary to posterior uveitis. The primary efficacy outcome is based on the change in disease status of the study eye from the period of assessment prior to implantation (34 weeks) to the 34-week period following implantation.

All patients entering the study were randomly assigned to one of two treatments, 0.59 mg or 2.1 mg fluocinolone acetonide intravitreal implant in the ratio of 1:1. Only one eye received an implant. In patients with unilateral disease, the affected eye was the study eye. In patients with bilateral disease

¹ 1= A ≥ 2 steps increase in A/C cells, 2= A ≥ 2 steps increase in the vitreous haze, and 3= A deterioration in visual acuity of at least 0.30 logMAR units from the screening baseline associated with recurrence of uveitis.

the study eye was the more severely affected eye, i.e., the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA or if equal, the eye clinically judged by the treating physician to be the more severely affected eye.

A total enrollment of approximately 250 patients was planned for this study. It was expected that approximately 100 patients would be recruited from India, 40 patients from Canada, 40 patients from Australia, 30 patients from the United States, 10 patients from Hong Kong, and 30 patients from the Philippines.

The objectives of this study were:

- To evaluate the safety and efficacy of intravitreal fluocinolone acetonide implants in the management of patients with non-infectious uveitis affecting the posterior segment of the eye.
- To compare the safety and efficacy of 2 doses of fluocinolone acetonide (0.59 or 2.1 mg) delivered by an intraocular/intravitreal implant in patients with non-infectious uveitis affecting the posterior segment of the eye.

Surgical implantation was to be performed on Day 1. The patient was to return to the study site on Day 2, Weeks 1 (+ 2 days), 4, 8, 12, 18, 24, 30 and 34 (+ 1 week) and for additional long-term follow-up visits approximately every 3 months (\pm 1 month) for a total duration of 3 years post-implantation. All assessments were made for both eyes of all patients, unless indicated differently.

The following assessments were to be made at each of these visits:

- Complete bilateral ophthalmic examination including visual acuity, intraocular pressure (recorded as the mean of three measurements), ophthalmoscopy, and slit lamp examination).
- Eliciting reports of adverse events occurring since the previous visit.
- At Week 34 (final study visit prior to long-term follow-up): interim medical history, physical examination, quality-of-life surveys (if validated in the patient's native language), and visual field. QOL surveys were also made at months 12, 24, and 36 after implantation.

3.1.2.2 Primary Efficacy Endpoint

The primary efficacy outcome was the change in recurrence of uveitis inflammation of the study eye from the period of assessment of 34 weeks prior to implantation to the period of assessment of 34 week following implantation.

- *Recurrence of uveitis Pre-implantation:* A recurrence with onset within 34 weeks prior to implantation is defined by the investigator's assessment that the patient satisfied the definition of a "protocol defined" recurrence as recorded on the Uveitis History CRF. This can be contradicted by a maximum anterior chamber cell score <2 , a maximum vitreous haze score <2 , and a maximum change in visual acuity <0.3 logMAR or Snellen equivalent.
- *Recurrence of uveitis Post-implantation:* The post-implantation criteria by the 34 week visit were scored on a protocol specified scale and defined as a change from baseline (screening). A post-implantation recurrence by the 34 week visit was defined by a ≥ 2 step increase compared to baseline in the number of cells in the anterior chamber per high power field and not attributable to conditions other than non-infectious posterior uveitis, or an increase in the vitreous haze of ≥ 2 steps compared to baseline not attributable to conditions other than non-infectious posterior uveitis, or a deterioration

in visual acuity of at least 0.30 logMAR units from baseline, not attributable to conditions other than non-infectious posterior uveitis, or failure ever to be observed after the 24-week visit.

For any eye not observed after the 24-week visit it was assumed, due to lack of evidence to the contrary, that the eye experienced a recurrence. The determination of post implantation recurrences was based on the visual acuity and slit-lamp examination findings.

3.1.2.3 Secondary Efficacy endpoint

The secondary end points were:

- Post-implantation recurrence of uveitis rate: within-patient comparison of eyes (implant vs. fellow)
- Time-to-recurrence: within-patient comparison of eyes (implant vs. fellow)
- Within-patient comparison of adjunctive treatment required, pre- versus post implantation
- Visual acuity: within-patient comparison of responding eyes (implant vs. fellow)
- Area of CME: within-patient comparison of responding eyes (implant vs. fellow)
- Post-implantation uveitis rate: between patient treatment group comparison
- Time-to-recurrence: between treatment group comparison
- Quality of life surveys

The analysis of efficacy was planned to take place when all patients have completed a 34 week period of post implantation.

3.1.2.4 Patients Analyzed

Intent-to-Treat Population: All enrolled patients who were implanted and had at least one post-implant examination were included in the intent-to-treat population (N = 239).

Reviewer's comment: A more conservative definition of ITT population is all enrolled patients who receive treatment. A total of 239 patients were enrolled in this study. All of these enrolled patients had at least one post-implant examination. Therefore, in this study the protocol defined ITT population is the same as from the more conservative definition stated above.

Evaluable Population: An evaluable population was defined by a technical review and other clinical evaluation.

Safety Population: All patients who received study medication comprised the safety population.

3.1.2.5 Disposition of Patients, Demography, and Baseline Disease Conditions

Disposition and demographic characteristics of ITT patients is given in Table 13 and 14, respectively in the appendix. A total of 239 patients were enrolled into this study. Of these, 233 (97.5%) completed 34 weeks of the study. Of the 6 patients not completing, there were no patients who dropped out for lack of efficacy. Five patients discontinued due to adverse events, including one patient died, and one was lost to follow-up. An additional patient died on study day 324.

The population had a mean age of 41 years, ranging from 12 to 92 years, was approximately 70% Asian, and approximately 56% female. Approximately 80% of the population had bilateral disease, and 74% were using systemic immuno modulatory therapy for control of uveitis prior to enrollment.

There were no statistically significant differences in demographics between treatments (all p-values were between 0.2213 to 0.9978).

3.1.2.6 Sample size determination and efficacy analysis

3.1.2.6.1 Determination of sample size

The sample size of approximately 250 patients (2.1 mg = 125, 0.59 mg = 125) was selected to supplement the total number of patients implanted, as part of a worldwide clinical strategy specified in the protocol, for the Sponsor's evaluation of safety and efficacy of the implant.

Reviewer's Comment: No formal sample size calculation was mentioned in the protocol. Also the enrolment was suspended due to the SARS epidemic in Asia. Therefore, the power of the test is not known.

3.1.2.6.2 Primary Efficacy Analysis

The primary efficacy outcome was based on the change in disease status of the study eye from the 34 weeks period of assessment prior to implantation to the 34 week period following implantation. Following the criteria of the Statistical Analysis Plan, if a patient experienced one or more pre-implantation recurrences, the patient was assigned a positive disease status, otherwise the disease status was negative. A positive post-implantation disease status was assigned if the patient suffered at least one recurrence or if the patient was never observed after the 24-week visit; otherwise it was negative.

The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups although tables summarize the result by dose as well. In addition a set of 2X2 tables showing pre versus post-implantation disease status by investigative site was developed to examine the homogeneity of outcome.

3.1.2.6.3 Handling of dropouts or missing data

For parameters measured on a continuous scale, analyses were performed on the 34- Week Last Observation Carried Forward (LOCF) scores, defined as the last score observed in the study up to and including the 34-Week visit. In the event that the 34- Week visit was missed, then the 34-Week LOCF score was the last value obtained prior to study day 245 (which is 35 weeks post-implantation, since it is noted that the end of the protocol-stated window for the 34-Week scheduled visit was 34 ± 1 week). For analyses assessing the occurrence of a condition, an analysis was performed on the 'Overall' time frame in which the occurrence of the condition is noted if it was present at any post-implantation study visit up to the 34-Week visit. In the event that the 34-Week visit was missed, then the Overall score noted the occurrence of the condition over the entire study up through study day 245. An exception to this imputation strategy was employed for the analysis of posterior uveitis. For any eye not observed after the 24- week visit, it was assumed due to lack of evidence to the contrary, that the eye experienced a recurrence.

3.1.2.6.4 Secondary Efficacy Analysis

Within-patient comparison of post-implantation recurrence of uveitis rate (implant vs. fellow eyes): The within-patient comparison of post-implantation recurrence rates between the treated and fellow non-treated eyes was used to support a claim of efficacy for the implant. The proportion of patients whose recurrence status is different between the two eyes was analyzed using McNemar's test for correlated

proportions. This outcome was based on the combined dose groups although tables summarized the result by dose as well. Two populations were analyzed: patients presenting with bilateral uveitis and all patients.

Time-to-recurrence Within-patient comparison of eyes (implant vs. fellow): The distribution of time to first post-implantation recurrence of uveitis was determined for the implant and fellow eyes. Eyes without a recurrence, as defined previously, were censored at their last observation. Kaplan-Meier plots were used descriptively. This outcome was based on the combined dose groups although tables summarized the result by dose as well. Two populations were analyzed: patients presenting with bilateral uveitis and all patients.

Within-patient comparison of eyes previously controlled with systemic medication, pre- versus post-implantation: Patients with bilateral disease that were treated systemically for control of their uveitis prior to enrollment were analyzed post implantation to determine freedom from systemic treatment with the implant vs. pre-implantation therapy. If a patient's posterior uveitis was being treated with systemic therapy at the time of enrollment, the patient was assigned a positive status, otherwise the status was negative.

A positive post-implantation status was assigned if the patient was receiving systemic therapy at the 34 week visit for control of non-infectious posterior uveitis; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups although tables summarized the result by dose as well.

Within patient comparison of patients receiving peri-ocular injections to control uveitis, pre- versus post-implantation: Patients entering the trial in which peri-ocular injections were used to control inflammation prior to implantation were compared pre and post implantation for freedom from the need for peri-ocular injections in the implanted eye. Additionally, comparison with the fellow eye for the need for peri-ocular injections was analyzed. If a patient received peri-ocular injections for the treatment of posterior uveitis during the 34 weeks prior to enrollment, the patient was assigned a positive status, otherwise the status was negative. A positive post-implantation status was assigned if the patient received peri-ocular injections during the 34 week period after implantation for control of non-infectious posterior uveitis; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups although tables summarized the result by dose as well.

Within patient comparison of patients receiving topical corticosteroids to control uveitis, pre- versus post-implantation: Patients entering the trial in which topical corticosteroids were used to control inflammation prior to implantation were compared pre and post implantation for freedom from the need for topical corticosteroids in the implanted eye. Additionally comparison with the fellow eye for the need for topical corticosteroids was analyzed. If a patient received topical ocular corticosteroids for the treatment of posterior uveitis during the 34 weeks prior to enrollment, the patient was assigned a positive status, otherwise the status was negative. A positive post-implantation status was assigned if the patient received topical ocular corticosteroids during the 34 week period after implantation for control of non-infectious posterior uveitis; otherwise it was negative.

The proportion of patients whose status has changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups although tables summarized the result by dose as well.

Visual Acuity: Within-patient Comparison of Responding Eyes (implant vs. fellow): A change of 0.3 logMAR (3 lines ETDRS) is generally accepted as being clinically significant. A positive response was assigned if the patient experienced at least a 3 line improvement in visual acuity at Week 34, otherwise the response was negative. Patients not observed at Week 34 were assigned a negative response. The proportion of patients whose response status was different between the two eyes was analyzed using McNemar's test for correlated proportions. Descriptive statistics on the observed VA and change from baseline scores are presented, as well as the distribution of change from baseline scores categorized by the number of lines gained and lost. This outcome was based on the combined dose groups, however tables summarized the result by dose as well. Two populations were analyzed: patients presenting with bilateral uveitis and all patients.

Area of CME Within-patient comparison of responding eyes (implant vs. fellow): The change from baseline in area of CME on the 300-second frame of the fluorescein angiogram at 34 weeks post-implantation in the implanted eye was compared to the fellow non-implanted eye in patients with bilateral disease at entry. A positive response was assigned if the measured area of CME on the 300-second frame of the angiogram at Week 34 was less than at baseline, otherwise the response was negative. Only patients observed at baseline and Week 34 were included in this analysis. The proportion of patients whose response status was different between the two eyes was analyzed using McNemar's test for correlated proportions. This outcome is based on the combined dose groups although tables summarized the result by dose as well. Two populations were analyzed: patients presenting with bilateral uveitis and all patients.

Post-implantation uveitis rate: Between treatment group comparison: The comparison of the treatment groups with respect to the proportion of patients who experienced a recurrence was performed using the Cochran-Mantel-Haenszel Chi-square test, stratified for study site and type of prior therapy.

Time-to-recurrence between treatment group comparison: The distribution of time to first post-implantation recurrence of uveitis in the implant eye was compared between treatment groups by proportional hazards regression stratified by investigative site and prior therapy. Eyes without a recurrence, as defined previously, were censored at their last observation. Kaplan-Meier plots were used descriptively.

Pre- versus post-implantation occurrence of intraocular inflammation based upon anterior chamber cells or vitreous haze: This outcome was based on the change in intraocular inflammation status of the study eye from the period of assessment prior to implantation (34 weeks) to the 34 week period following implantation. For the pre-implantation period a score ≥ 2 for anterior chamber cells or vitreous haze, the patient was assigned a positive intraocular inflammatory status, otherwise the status was negative. For the post-implantation period, a positive status was assigned if the patient experienced an increase in anterior chamber cells or vitreous haze ≥ 2 or if the patient was never observed after the 24-week visit; otherwise it was negative. The proportion of patients whose status changed was analyzed using McNemar's test for correlated proportions. This outcome was based on the combined dose groups although tables summarized the result by dose as well.

Quality of life surveys: The quality-of-life survey was evaluated using the SF-36, VFQ-25, and VFQ-37 scores. The sub-scale and the composite scale data were summarized using descriptive statistics. Continuous variables were analyzed using the paired t-test and categorical variables were analyzed using the Wilcoxon signed-rank test.

3.1.2.6.5 Safety Analysis

Safety variables contributing to the safety outcomes analysis are: IOP, lens opacity scores, visual field, adverse events, concomitant medication, vital signs, clinical laboratory value changes, ERG (selected centers), visual acuity and ophthalmoscopic examination findings.

The proportion of patients reporting adverse events grouped by MedDRA, including signs of local (ocular) toxicity (e.g., vitreous hemorrhage, retinal detachment, cataract, endophthalmitis, drug toxicity), and post-operative complications was tabulated. For ocular events, separate tabulations were made for the implant and fellow eyes. Comparisons of proportions between dose groups of patients experiencing one or more events classified to the primary preferred term in MedDRA were tested by Fisher's exact test.

3.1.2.7 Sponsor's Results and Conclusions

3.1.2.7.1 Primary efficacy outcome

A summary of uveitis recurrence during the 34-week period prior to, and during the 34-week period subsequent to implantation is shown in Table 15 in the appendix. For both doses combined, 37.7% (90/239) had recurrences during the period prior to implantation, while 11.7% (28/239) presented with recurrences during the period subsequent to implantation ($p < 0.0001$). The efficacy results from "as randomized" population was the same as those of "as treated" population.

3.1.2.7.2 Secondary efficacy outcome

Uveitis recurrence fellow eyes: A summary of uveitis recurrence during the 34-week period prior to, and during the 34-week period subsequent to implantation is shown in Table 16 in the appendix. One fellow eye (2.1 mg group) was prosthetic, and thus the sample size is 238 eyes. For both doses combined, 14.3% (34/238) had recurrences during the period prior to implantation, while 47.9% (114/238) presented with recurrences during the period subsequent to implantation ($p < 0.0001$). One patient was not seen after the week 24 visit, and thus was counted as a recurrence.

Within-patient comparison of post-implantation recurrence of uveitis rate (implant vs. fellow eyes): A summary of uveitis recurrence during the 34-week period prior to, and during the 34-week period subsequent to implantation is shown in Table 17 in the appendix. For both doses, 11.7% (28/239) of study eyes had recurrences during the period subsequent to implantation, while 47.9% (114/238) of fellow eyes had recurrences during this period ($p < 0.0001$).

Time-to-recurrence: Within-patient comparison of eyes (implant vs. fellow): The time-to-recurrence of uveitis for implant vs. fellow eyes was evaluated by Kaplan-Meier methods (freedom from recurrence). Figures 2A and Figure 2B in the appendix show the Kaplan-Meier curves for 0.59 mg and 2.1 mg treatment groups. The plots show, in both dose groups, uveitis recurred in the fellow eyes sooner than implanted eyes. An additional analysis comparing study vs. fellow eyes for the ITT population with bilateral disease was supportive of this analysis.

Visual Acuity Within-patient Comparison of Responding Eyes (implant vs. fellow): The proportion of patients with an improvement in visual acuity in study eyes vs. fellow eyes at week 34 is shown in Table 18 in the appendix. For both doses combined, 19.0% (44/231) of study eyes improved by at least 0.30 logMAR, while 6.6% (15/228) of fellow eyes improved by the same criterion ($p < 0.0001$).

Area of CME Within-patient comparison of eyes with a decrease in CME (300 sec) (implant vs. fellow): Patients underwent fluorescein angiography at screening, week 8 and week 34. This analysis was masked to study subjects and Investigators. The proportion of patients with an improvement in the area of CME at week 34 is shown in Table 19 in the appendix. For both doses, 69.2% (72/104) of study eyes improved, while 23.1% (24/104) of fellow eyes improved ($p < 0.0001$). An analysis of eyes with bilateral disease at baseline provided similar results.

Post-implantation uveitis rate between treatment group comparison: The uveitis recurrence rate by dose group is shown in Table 20 in the appendix. The rate in the 0.59 mg group study eyes, 13.7% (16/117) was similar to that seen in the 2.1 mg group, 9.8% (12/122, $p = 0.5773$).

Time-to-recurrence between treatment group comparison: An analysis of the freedom from recurrence of uveitis between treatments was performed using a proportional hazard model, stratified by site and prior therapy. The hazard ratio between doses was 0.813 (95% C.I., 0.366 – 1.805; $p = 0.6112$).

Pre- versus post-implantation occurrence of intraocular inflammation based upon anterior chamber cells or vitreous haze Study eyes: A summary of intraocular inflammation during the 34-week period prior to, and during the 34-week period subsequent to implantation (including any post-operative periods) is shown in Table 21 in the appendix. For both doses, 61.1% (146/239) had intraocular inflammation during the period prior to implantation, while 43.5% (104/239) presented with intraocular inflammation during the period subsequent to implantation ($p = 0.0001$).

Pre- versus post-implantation occurrence of intraocular inflammation based upon anterior chamber cells or vitreous haze Fellow eyes: A summary of intraocular inflammation during the 34-week period prior to, and during the 34-week period subsequent to implantation (including any post-operative periods) is shown in Table 22. For both doses, 27.3% (65/238) had intraocular inflammation during the period prior to implantation, while 42.4% (101/238) presented with intraocular inflammation during the period subsequent to implantation ($p = 0.0001$).

Other secondary out comes: Other secondary out comes such as Within-patient comparison of eyes previously controlled with systemic medication, at enrollment vs. at 34 weeks post-implantation, within-patient comparison of patients receiving peri-ocular injections to control uveitis, pre- versus post-implantation in both Study eyes and Fellow eyes, and Within patient comparison of patients receiving topical corticosteroids to control uveitis, at enrollment vs. 34 weeks post-implantation in both Study eyes and Fellow eyes also showed significant results in favor of the study drug.

Quality of life surveys: At study entry, mean (\pm S.D.) measures for SF-36 (Physical composite), SF-36 (Mental composite), VFQ-25 composite and VFQ-37 composite were 48.8 ± 8.4 , 49.5 ± 10.0 , 68.5 ± 19.6 , and 69.3 ± 19.5 , respectively (scale of 0-100). To assess the effect of the implant on change in health-related and vision targeted quality of life, preoperative sub-scale and composite scores of the SF-36, VFQ-25 and VFQ-37 were subtracted from visit 11 (Week 34) follow-up scores.

For the SF-36, mean scores were mostly lower at follow-up indicating decreased health status. Although scores were lower, the only statistically significant ($p < 0.05$) mean change scores were for the general health perceptions sub-scale and the physical health composite. The general health perceptions follow-up mean score was approximately six points lower than the baseline mean score. The physical health composite mean score declined by less than three points. One sub-scale, emotional health problems, showed a mean increase of over ten points. However, this difference was not statistically significant. For the VFQ-25 and VFQ-37, mean changes were in the positive

direction (better vision targeted health status) and statistically significant for many of the sub-scales and for both of the composites. For the VFQ-25, significant mean change scores ranged from 5.6 to 13.0 points, with a mean change of 5.6 points for the VFQ-25 composite. The greatest change (13.0 points) was found for the sub-scale measuring mental health symptoms due to vision. For the VFQ-37, significant mean change scores ranged from 5.9 to 13.0 points, with a mean change of 6.0 points for the VFQ-37 composite. Results for the VFQ-37 were very similar to the VFQ-25.

3.1.2.8 Reviewer's Findings and Conclusions

This reviewer reanalyzed the primary efficacy variable. In the submitted data set "UVHIST" the variable RECURYN represents the presence or absence of protocol defined pre-treatment UV-recurrence. In this reviewer's analyses if RECURYN had a value 'Y' the pre-treatment recurrence was assumed to be positive. Also the submitted data set "UVRECUR" has variables RCODE and ONSETDT. The RCODE has 3 values (1, 2, and 3) representing the severity of UV-recurrence, while the ONSETDT shows the onset dates. In some cases while the onset date was present the severity was not mentioned i.e. RCODE was empty. In this reviewer's analysis if an onset date was present UV-recurrence was assumed to be positive regardless of the information of its severity. Data were analyzed using the McNemars's test on ITT population. Table 23 in the appendix shows this reviewer's analysis. There are some discrepancies between this reviewer's count of number of patients with positive UV-recurrence in both pre and post treatment. However, the general conclusion agreed with those of the sponsor i.e. both doses of Fluocinolone Acetonide showed statistically significantly low post-treatment UV-recurrence compared to pre-treatment UV-recurrence.

3.2 EVALUATION OF SAFETY

3.2.1 SPONSOR'S ANALYSIS OF SAFETY DATA

3.2.1.1 Study #BLP 415-001

Safety variables contributing to the safety outcomes analysis were: IOP, lens opacity scores, visual field, adverse events, concomitant medication, vital signs, clinical laboratory value changes, ERG (selected centers), visual acuity and ophthalmoscopic examination findings.

The proportion of patients reporting adverse events grouped by MedDRA, including signs of local (ocular) toxicity (e.g., vitreous hemorrhage, retinal detachment, cataract, endophthalmitis, drug toxicity), and post-operative complications was tabulated. For ocular events, separate tabulations were made for the implant and fellow eyes.

Treatment emergent ocular adverse events were reported in the study eye for 94.6% (263/278) of patients (1623 events), and in the fellow eye for 68.7% (191/278) of patients (553 events). The most frequently observed ocular adverse events in the study eye were increased intraocular pressure 51.8% (144/278), eye pain 27.0% (75/278), conjunctiva hemorrhage 26.6% (74/278), and conjunctival hyperemia 22.3% (62/278). Cataracts (grouped at the Higher Level Term) were seen in 28.8% (80/278) of study eyes. The most frequently observed ocular adverse events in the fellow eye were cataracts (grouped at the Higher Level Term), 14.4% (40/278), vitreous floaters 11.9% (33/278), and increased intraocular pressure 9.7% (27/278). Non-ocular adverse events were reported by 77.7% (216/278) of patients (814 events). The most frequently observed adverse events were headache NOS (20.5%, 57/278), nasopharyngitis (8.6%, 24/278), nausea (8.6%, 24/278), and sinusitis NOS

(7.2%, 20/278). The incidence of adverse events was compared between the treatment groups using Fisher's exact test. Using the conservative threshold of $p=0.150$, the two treatment groups differed for the following preferred terms: Study eye: eye pain, eye inflammation NOS, conjunctivitis, photopsia, ptosis, hyphema, scotoma, burning, eyelid movement disorders; Fellow eye: cataract NOS and IOP elevation. However, the direction of these comparative incidences was variable, in some cases being greater in the 0.59 mg group, and in other cases being greater in the 2.1 mg group. The most frequent serious adverse event was cataracts (either aggravated or *de novo*) which was seen in 13.3% (37/278) of study eyes and in 4.0% (11/278) in fellow eyes. Also frequently observed in the study eye was elevation of IOP 6.5% (18/278) and/or glaucoma (any type, 8.3%, 23/278). There were no deaths through 34 weeks of study participation. Patient 132-1086 completed the 34 week visit on 20 March 2002, and subsequently died on 18 April 2002 due to cancer. Treatment emergent ocular adverse events were reported in the study eye for 94.6% (263/278) of patients (1623 events), and in the fellow eye for 68.7% (191/278) of patients (553 events). The most frequently observed ocular adverse events in the study eye were increased intraocular pressure 51.8% (144/278), eye pain 27.0% (75/278), conjunctival hemorrhage 26.6% (74/278), and conjunctival hyperemia 22.3% (62/278). Cataracts (grouped at the Higher Level Term) were seen in 28.8% (80/278) of study eyes. The most frequently observed ocular adverse events in the fellow eye were cataracts (grouped at the Higher Level Term), 14.4% (40/278), vitreous floaters 11.9% (33/278), and increased intraocular pressure 9.7% (27/278).

The most frequent ocular adverse events are shown in Table 24. There were 27 (24.6%), 39 (35.5%), and 35 (31.8%) of patients with mild, moderate and severe ocular events in the study eye in the 0.59 mg group, and 55 (32.7%), 72 (42.9%) and 35 (20.8%) in the 2.1 mg group, respectively. There were 6 (5.5%), 8 (7.3%) and 87 (79.1%) of patients with unrelated, unlikely and possibly/probably related ocular events in the study eye in the 0.59 mg group, and 17 (10.1%), 13 (7.7%), and 132 (78.6%) in the 2.1 mg group, respectively.

3.2.1.2 Study #BLP 415-004

Treatment emergent ocular adverse events were reported in the study eye for 97.1% (232/239) of patients (1874 events), and in the fellow eye for 63.2% (151/239) of patients (428 events). The most frequent ocular adverse events are shown in Table 25. The most frequently observed ocular adverse events in the study eye were increased intraocular pressure 54.4% (130/239), eye pain 41.8% (100/239), and visual acuity decreased 35.6% (85/239). Cataracts (grouped at the Higher Level Term) were seen in 38.9%, (93/239) of the study eyes.

The most frequently observed ocular adverse events in the fellow eye were cataracts (grouped at the Higher Level Term); 18.4% (44/239), visual acuity reduced 15.1% (36/239) and eye pain 10.0% (24/239). Non-ocular adverse events were reported by 74.5% (178/239) of patients (658 events). The most frequently observed non-ocular adverse events were headache NOS 19.3% (46/239), pyrexia 10.9% (26/239), arthralgia 8.4% (20/239), nasopharyngitis 9.2% (22/239), dizziness 7.1% (17/239), cough 6.7% (16/239), vomiting 6.3% (15/239) and influenza 5.4% (13/239).

The most frequent serious adverse event was cataracts (aggravated, *de novo*, or posterior capsule opacification) which was seen in 15.9% (38/239) of study eyes and in 7.5% (18/239) of fellow eyes. Also frequently observed in the study eye was elevation of IOP 8.8% (21/239) and/or glaucoma (any type) 5.0% (12/239). There were two deaths in this study. Subject 244855-1254 (0.59 mg treatment group) died on study day 49 due to an abdominal aortic aneurysm. Subject 154949-2028 (2.1 mg treatment group) died on study day 324 (past 34 weeks) due to sudden cardiac death. Neither death was reported to be related to the study drug.

3.2.2 REVIEWER'S ANALYSIS OF SAFETY DATA

This reviewer did not perform any analysis on the safety data. This reviewer refers to the clinical review for safety analysis.

4 FINDINGS IN SPACIAL/SUBGROUP POPULATIONS

4.1 SPONSOR'S SUB-GROUP ANALYSIS

4.1.1 STUDY #BLP 415-001

4.1.1.1 *Sub-group analysis by Age*

The sponsor analyzed the key efficacy and safety measures stratifying by age (< 65, 65 to <75 and ≥75 years). Table 26 in the appendix shows the results.

4.1.1.2 *Sub-group analysis by Gender*

The sponsor analyzed the key efficacy and safety measures stratifying by gender. Table 27 in the appendix shows the results.

4.1.1.3 *Sub-group analysis by Race*

The sponsor analyzed the key efficacy and safety measures stratifying by race. Table 28 in the appendix shows the results.

4.1.1.4 *Analysis by Other Special/Subgroup populations*

The sponsor analyzed the data sub grouping by iris color. Tables 29 in the appendix show the results.

4.1.2 STUDY #BLP 415-004

4.1.2.1 *Sub-group analysis by Age*

The sponsor analyzed the key efficacy and safety measures stratifying by age (< 65, 65 to <75 and ≥75 years). Table 30 in the appendix shows the results.

4.1.2.2 *Sub-group analysis by Gender*

The sponsor analyzed the key efficacy and safety measures stratifying by gender. Table 31 in the appendix shows the results.

4.1.2.3 *Sub-group analysis by Race*

The sponsor analyzed the key efficacy and safety measures stratifying by race. Table 32 in the appendix shows the results.

4.1.2.4 *Analysis by Other Special/Subgroup populations*

The sponsor analyzed the data sub grouping by iris color. Tables 33 in the appendix show the results.

4.2 REVIEWER'S SUB-GROUP ANALYSIS

This reviewer also performed subgroup analysis by age, gender, and race following similar data selection process as was followed in his primary efficacy analysis. Tables 34 and 35 show this reviewer's results for Studies #BLP 415-001 and #BLP 415-004, respectively. Most of the sub-group by gender, age, race, and iris color showed statistically significant effects for both dose groups in spite of their small sample sizes.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

In this submission the sponsor included reports of two completed Phase 3 studies, namely Studies # BLP 415-001 and # BLP 415-004 to establish the efficacy of Intravitreal Fluocinolone Acetonide Implant (0.59 or 2.1 mg) by reducing the recurrence of uveitis inflammation in patients with non-infectious uveitis Affecting the posterior segment of the eye. The sponsor also included partial information and/or the protocols of four other studies, namely _____ . These studies are either on-going or extension into compassionate use of the first two completed studies, and therefore not reviewed here. This reviewer's report is based only on data of the two completed studies, namely Studies # BLP 415-001 and # BLP 415-004.

Results from Studies # BLP 415-001 and # BLP 415-004 showed that patients in both 0.59 and 2.1 mg of Fluocinolone Acetonide Implant dose groups had statistically significant reduction in the recurrence of uveitis inflammation in patients with non-infectious uveitis affecting the posterior segment of the eye. Almost all secondary efficacy endpoints also showed favorable results (some of them were statistically significant). Most of the sub-group by gender, age, race, and iris color showed statistically significant effects for both dose groups in spite of their small sample sizes.

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5.2 CONCLUSIONS AND RECOMMENDATIONS

Results from the two completed studies showed that patients in both 0.59 and 2.1 mg of Fluocinolone Acetonide Implant dose groups had statistically significant reduction in the recurrence of uveitis inflammation in patients with non-infectious uveitis affecting the posterior segment of the eye. However, due to the absence of any control group in both studies a comparative statement on efficacy could not be made.

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6 APPENDIX

Table 1
 Patient Disposition
 (Study # BLP 415-001)

<i>Population</i>	<i>Treatment group</i>		<i>Total</i>
	<i>0.59 mg</i>	<i>2.1 mg</i>	
Entered	110	168	278
Completed	106 (96.4%)	165 (98.2%)	271 (97.5%)
Discontinued	4 (3.6%)	3 (1.8%)	7 (2.5%)
Efficacy failure	---	---	---
Adverse events	2 (1.8%)	1 (0.6%)	3 (1.1%)
Protocol violation	---	1 (0.6%)	1 (0.4%)
Lost to follow-up	2 (1.8%)	1 (0.6%)	3 (1.1%)
Death	---	---	---

Source: Table 4 of sponsor's analysis

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Table 2
Demographic and Baseline Characteristics
Study #BLP 415-001

Measure		Treatment group			P-value
		0.59 mg	2.1 mg	All	
Age					
	N	110	168	278	
	Mean	44.72	42.77	43.54	0.3063
	Std	17.02	14.37	15.47	
	Min	7.00	9.00	7.00	
	Max	84.00	76.00	84.00	
	< 65	97 (88.2%)	155 (92.3%)	252	
	65-<75	5 (4.6%)	12 (7.1%)	17	
	≥75	8 (7.3%)	1 (0.6%)	9	
Race					
	Caucasian	75 (68.2%)	109 (64.9%)	184	0.7214
	Black	19 (17.3%)	30 (17.9%)	49	
	Asian	9 (8.2%)	12 (7.1%)	21	
	Hispanic	4 (3.6%)	13 (7.7%)	17	
	Other	3 (2.7%)	4 (2.4%)	7	
Gender					
	Male	29 (26.4%)	48 (28.6%)	77	0.6875
	Female	81 (73.6%)	120 (71.4%)	201	
Iris color					
	Brown	62 (56.4%)	96 (57.1%)	158	0.9932
	Hazel	16 (14.6%)	27 (16.1%)	43	
	Green	7 (6.4%)	10 (6.0%)	17	
	Blue	23 (20.9%)	32 (19.1%)	55	
	Other	2 (1.8%)	3 (1.8%)	5	
Laterality of uveitis					
	Unilateral	26 (23.6%)	38 (22.6%)	64	0.8438
	Bilateral	84 (76.4%)	130 (77.4%)	214	
Previous uveitis treatment					
	Systemic	68 (61.8%)	114 (67.9%)	182	0.3004
	Local	42 (38.2%)	54 (32.1%)	96	

Source: Table 6 of sponsor's analysis

Table 3
Sample Size Calculations
Study #BLP 415-001

Pr(recurrence) in 2.1 mg group	1%	10%	15%	20%	25%
Pr(recurrence) in 0.59 mg group	12%	27%	34%	40%	46%

Source: Table 3 of sponsor's analysis

Assuming N in the 2.1 mg group = 150, and N in the 0.59 mg group = 100, for a total of 250 subjects:

Table 4
Uveitis Recurrence in Study Eye in Intent-to-treat patients as Treated
Study #BLP 415-001

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	110	60 (54.6%)	7 (6.4%)	<0.0001
2.1 mg	168	83 (49.4%)	10 (6.0%)	<0.0001
Both doses	278	143 (51.4%)	17 (6.1%)	<0.0001

Source: Table 9 of sponsor's analysis

Table 5
Uveitis recurrence in Fellow Eyes in Intent-to-treat patients as treated
Study #BLP 415-001

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	109	26 (23.9%)	45 (41.3%)	0.0009
2.1 mg	167	30 (18.0%)	71 (42.5%)	<0.0001
Both doses	276	56 (20.3%)	116 (42.0%)	<0.0001

Source: Table 10 of sponsor's analysis

Table 6
Post-Implantation Recurrences of Uveitis Within-Eye Comparison of Study
Eye Versus Fellow Eye in Intent-to-Treat Patients
Study #BLP 415-001

<i>Dose</i>	<i>Study eyes Recurrence</i>		<i>Fellow eyes Recurrence</i>		<i>P-value</i> ¹
	<i>N</i>		<i>N</i>		
0.59 mg	110	7 (6.4%)	109	45 (41.3%)	< 0.0001
2.1 mg	168	10 (6.0%)	167	71 (42.5%)	< 0.0001
Both doses	278	17 (6.1%)	276	116 (42.0%)	< 0.0001

Source: Table 11 of sponsor's analysis

Table 7
Incidence of Improvement in Visual Acuity from Baseline of At Least 0.30 logMAR
at Week 34 in intent to treat population
Study #BLP 415-001

<i>Dose</i>	<i>Study eyes Improvement</i>		<i>Fellow eyes Improvement</i>		<i>P-value</i> ¹
	<i>N</i>		<i>N</i>		
0.59 mg	104	20 (19.2%)	102	7 (6.9%)	0.0016
2.1 mg	163	36 (22.1%)	163	9 (5.5%)	< 0.0001
Both doses	267	56 (21.0%)	265	16 (6.0%)	< 0.0001

Source: Table 17 of sponsor's analysis

Table 8
Incidence of Reduction in the Area of CME of the Fluorescein Angiogram Between
Baseline and 34 weeks in Intent to Treat Population
Study #BLP 415-001

<i>Dose</i>	<i>N</i>	<i>Study eyes</i>	<i>Fellow eyes</i>	<i>P-value</i> ¹
0.59 mg	43	33 (76.7%)	14 (32.6%)	< 0.0001
2.1 mg	71	48 (67.6%)	14 (19.7%)	< 0.0001
Both doses	114	81 (71.1%)	28 (24.6%)	< 0.0001

Source: Table 18 of sponsor's analysis

Table 9
Summary of post-implantation recurrences of uveitis in Intent to Treat Population
Study #BLP 415-001

	<i>0.59 mg Dose</i>		<i>2.1 mg Dose</i>		<i>Both doses</i>	
	<i>Study</i>	<i>Fellow</i>	<i>Study</i>	<i>Fellow</i>	<i>Study</i>	<i>Fellow</i>
<i>N</i>	110	109	168	167	278	276
<i>Incidence</i>	7	45	10	71	17	116
<i>Percent</i>	6.4%	41.3%	6.0%	42.5%	6.1%	42.0%

Source: Table 19 of sponsor's analysis

Table 10
Intraocular inflammation regardless of causality Pre- vs. post implantation
Occurrence in Intent-to-treat population: Study eyes
Study #BLP 415-001

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	110	64 (58.2%)	64 (58.2%)	1.0000
2.1 mg	168	85 (50.6%)	89 (53.0%)	0.6733
Both doses	278	149 (53.6%)	153 (55.0%)	0.7371

Source: Table 20 of sponsor's analysis

Table 11
Intraocular Inflammation Regardless of Causality Pre- vs. Post Implantation
Occurrence in Intent-to-Treat Population: Fellow eyes
Study #BLP 415-001

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	109	28 (25.7%)	56 (51.4%)	0.0001
2.1 mg	167	43 (25.8%)	75 (44.9%)	0.0002
Both doses	276	71 (25.7%)	131 (47.5%)	<0.0001

Source: Table 21 of sponsor's analysis

Table 12
Uveitis Recurrence in Study Eye in Intent-to-treat patients as Treated
Study #BLP 415-001
(Reviewer's Table)

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	110	61 (55.5%)	6 (5.45%)	<0.0001
2.1 mg	168	90 (53.6%)	10 (6.0%)	<0.0001
Both doses	278	151 (54.3%)	16 (5.8%)	<0.0001

Table 13
Patient disposition at 34 weeks
Study #BLP 415-004

<i>Population</i>	<i>Treatment group</i>		<i>Total</i>
	<i>0.59 mg</i>	<i>2.1 mg</i>	
Entered	117	122	239
Completed	114 (97.4%)	119 (97.5%)	233 (97.5%)
Discontinued	3 (2.6%)	3 (2.5%)	6 (2.5%)
Efficacy failure	---	---	---
Adverse events	2 (1.7%)	3 (2.5%)	5 (2.1%)
Death	1 (0.9%)	---	1 (0.4%)
Lost to follow-up	1 (0.9%)	---	1 (0.4%)

Source: Table 2 of Sponsor's analysis
 2122*, 2124, 1011, 1205, 2139, and 1254

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Table 14
Demographic and other baseline characteristics: All randomized population
Study #BLP 415-004

<i>Measure</i>	<i>Treatment group</i>			<i>P-value</i>
	<i>0.59 mg</i>	<i>2.1 mg</i>	<i>All</i>	
Age				
N	117	122	239	
Mean	42.48	40.37	41.40	0.2213
Std	14.07	12.51	13.31	
Min	12.00	15.00	12.00	
Max	74.00	92.00	92.00	
< 65	106 (90.6%)	118 (96.7%)	224	
65-<75	11 (9.4%)	2 (1.6%)	13	
≥75	---	2 (1.6%)	2	
Race				
Caucasian	24 (20.5%)	28 (23.0%)	52	0.9770
Black	3 (2.6%)	4 (3.3%)	7	
Asian	83 (70.9%)	84 (68.9%)	167	
Hispanic	2 (1.7%)	2 (1.6%)	4	
Other	5 (4.3%)	4 (3.3%)	9	
Gender				
Male	47 (40.2%)	58 (47.5%)	105	0.2511
Female	70 (59.8%)	64 (52.5%)	134	
Iris color				
Brown	89 (76.1%)	91 (74.6%)	180	0.6574
Hazel	3 (2.6%)	7 (5.7%)	10	
Green	2 (1.7%)	4 (3.3%)	6	
Blue	11 (9.4%)	9 (7.4%)	20	
Other	12 (10.3%)	11 (9.0%)	23	
Laterality of uveitis				
Unilateral	23 (19.7%)	24 (19.7%)	47	0.9978
Bilateral	94 (80.3%)	98 (80.3%)	192	
Previous uveitis treatment				
Systemic	89 (76.1%)	87 (71.3%)	176	0.4041
Local	28 (23.9%)	35 (28.7%)	63	

Source: Table 4 of Sponsor's analysis
 P-value for continuous measures by ANOVA, and for categorical measures by Chi-Square test.

Table 15
 Uveitis recurrence: 34 week periods prior to, and subsequent to implantation
 Intent-to-treat patients Study eyes As treated
 Study #BLP 415-004

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	117	46 (39.3%)	16 (13.7%)	<0.0001
2.1 mg	122	44 (36.1%)	12 (9.8%)	<0.0001
Both doses	239	90 (37.7%)	28 (11.7%)	<0.0001

Source: Table 7 of Sponsor's analysis
 P-value is from McNemar's test.

Table 16
 Uveitis recurrence: 34 week periods prior to, and subsequent to
 implantation: Intent-to-treat patients: Fellow eyes: As treated
 Study #BLP 415-004

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	117	18 (15.4%)	57 (48.7%)	<0.0001
2.1 mg	121	16 (13.2%)	57 (47.1%)	<0.0001
Both doses	238	34 (14.3%)	114 (47.9%)	<0.0001

Source: Table 8 of Sponsor's analysis
 P-value is from McNemar's test.

Table 17
 Post-implantation recurrences of uveitis within-treatment comparison of
 study eye versus fellow eye: Intent-to-treat patients
 Study #BLP 415-004

<i>Dose</i>	<i>Study eyes Recurrence</i>		<i>Fellow eyes Recurrence</i>		<i>P-value</i> ¹
	<i>N</i>		<i>N</i>		
0.59 mg	117	16 (13.7%)	117	57 (48.7%)	< 0.0001
2.1 mg	122	12 (9.8%)	121	57 (47.1%)	< 0.0001
Both doses	239	28 (11.7%)	238	114 (47.9%)	< 0.0001

Source: Table 9 of Sponsor's analysis
 P-value is from McNemar's test.

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Table 18
Incidence of improvement in visual acuity from baseline of at least 0.30 logMAR at Week 34
Intent to treat population
Study #BLP 415-004

Dose	N	Study eyes	N	Fellow eyes	P-value ¹
0.59 mg	112	24 (21.4%)	112	11 (9.8%)	0.0158
2.1 mg	119	20 (16.8%)	116	4 (3.5%)	0.0002
Both doses	231	44 (19.0%)	228	15 (6.6%)	< 0.0001

Source: Table 15 of Sponsor's analysis
 P-value is from McNemar's test.

Table 19
Incidence of reduction in the area of CME of the fluorescein angiogram
between baseline and 34 weeks: Intent to treat population
Study #BLP 415-004

Dose	N	Study eyes	Fellow eyes	P-value ¹
0.59 mg	55	39 (70.9%)	14 (25.5%)	< 0.0001
2.1 mg	49	33 (67.4%)	10 (20.4%)	< 0.0001
Both doses	104	72 (69.2%)	24 (23.1%)	< 0.0001

Source: Table 16 of Sponsor's analysis
 P-value is from McNemar's test.

Table 20
Summary of post-implantation recurrences of uveitis: Intent to Treat Population
Study #BLP 415-004

	0.59 mg Dose		2.1 mg Dose		Both doses	
	Study	Fellow	Study	Fellow	Study	Fellow
n	117	117	122	121	239	238
Incidence	16	57	12	57	28	114
Percent	13.7%	48.7%	9.8%	47.1%	11.7%	47.9%

Source: Table 17 of Sponsor's analysis
 p-value by CMH = 0.5773

Table 21
Intraocular inflammation regardless of causality: Pre- vs. post implantation occurrence: Intent-to-treat
population: Study eyes
Study #BLP 415-004

Dose	N	Pre-implant	Post-implant	P-value ¹
0.59 mg	117	77 (65.8%)	54 (46.2%)	0.0028
2.1 mg	122	69 (56.6%)	50 (41.0%)	0.0167
Both doses	239	146 (61.1%)	104 (43.5%)	0.0001

Source: Table 18 of Sponsor's analysis
 P-value is from McNemar's test.

Table 22
Intraocular inflammation regardless of causality: Pre- vs. post
implantation occurrence: Intent-to-treat population: Fellow eyes
Study #BLP 415-004

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	117	34 (29.1%)	52 (44.4%)	0.0035
2.1 mg	121	31 (25.6%)	49 (40.5%)	0.0094
Both doses	238	65 (27.3%)	101 (42.4%)	0.0001

Source: Table 19 of Sponsor's analysis
¹ P-value is from McNemar's test.

Table 23
Uveitis Recurrence in Study Eye in Intent-to-treat patients as Treated
Study #BLP 415-004
(Reviewer's Table)

<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value</i> ¹
0.59 mg	117	33 (28.2%)	10 (8.65%)	0.0002
2.1 mg	122	36 (29.5%)	10 (8.2%)	<0.0001
Both doses	239	69 (28.9%)	20 (8.37)	<0.0001

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Table 24
Summary of adverse events: Ocular (Most frequent > 5% in either dose)
Study #BLP 415-001

Preferred term	0.59 mg			2.1 mg			Both doses		
	Pts	%	Events	Pts	%	Events	Pts	%	Events
<i>Study eye</i>									
Intraocular pressure increased	54	49.09	80	90	53.57	123	144	51.80	203
Eye pain	23	20.91	35	52	30.95	69	75	26.98	104
Conjunctival haemorrhage	29	26.36	32	45	26.79	49	74	26.62	81
Conjunctival hyperaemia	22	20.00	23	40	23.81	44	62	22.30	67
Pain NOS	16	14.55	19	32	19.05	46	48	17.27	65
Visual acuity reduced	20	18.18	21	27	16.07	31	47	16.91	52
Postoperative complications NOS	20	18.18	21	27	16.07	28	47	16.91	49
Cataract NOS aggravated	16	14.55	18	27	16.07	28	43	15.47	46
Eye irritation	14	12.73	15	28	16.67	37	42	15.11	52
Eye pruritus	17	15.45	19	21	12.50	24	38	13.67	43
Vitreous floaters	16	14.55	16	21	12.50	27	37	13.31	43
Abnormal sensation in eye	13	11.82	15	23	13.69	27	36	12.95	42
Vision blurred	14	12.73	17	21	12.50	23	35	12.59	40
Postoperative wound complication NOS	15	13.64	17	19	11.31	22	34	12.23	39
Vitreous haemorrhage	17	15.45	17	16	9.52	18	33	11.87	35
Maculopathy	13	11.82	17	18	10.71	22	31	11.15	39
Hypotony of eye	9	8.18	10	17	10.12	18	26	9.35	28
Cataract NOS	9	8.18	9	17	10.12	17	26	9.35	26
Eyelid ptosis	6	5.45	6	20	11.90	22	26	9.35	28
Glaucoma NOS	9	8.18	10	15	8.93	16	24	8.63	26
Macular oedema	10	9.09	12	11	6.55	11	21	7.55	23
Photophobia	9	8.18	9	11	6.55	11	20	7.19	20
Optic nerve cupping	10	9.09	11	8	4.76	9	18	6.47	20
Eyelid oedema	7	6.36	7	8	4.76	8	15	5.40	15
Vision abnormal loss	3	2.73	3	9	5.36	11	12	4.32	14
Photopsia	2	1.82	2	11	6.55	12	13	4.68	14
<i>Fellow eye</i>									
Vitreous floaters	15	13.64	20	18	10.71	23	33	11.87	43
Intraocular pressure increased	5	4.55	5	22	13.10	23	27	9.71	28
Vision blurred	11	10.00	12	14	8.33	15	25	8.99	27
Macular oedema	8	7.27	11	15	8.93	18	23	8.27	29
Visual acuity reduced	8	7.27	10	14	8.33	17	22	7.91	27
Eye pain	9	8.18	9	9	5.36	14	18	6.47	23
Cataract NOS aggravated	8	7.27	10	8	4.76	8	16	5.76	18
Cataract NOS	3	2.73	3	13	7.74	14	16	5.76	17
Maculopathy	7	6.36	7	8	4.76	8	15	5.40	15
Vitreous opacities	5	4.55	7	9	5.36	16	14	5.04	23
Eye pruritus	6	5.45	6	7	4.17	7	13	4.68	13

Source: Table 26 of sponsor's analysis

Table 25
Summary of adverse events: Ocular (Most frequent > 5% in either dose)
Study #BLP 415-004

Preferred term	0.59 mg			2.1 mg			Both doses		
	Pts	%	Events	Pts	%	Events	Pts	%	Events
<i>Study eye</i>									
Intraocular pressure increased	63	53.85	102	67	54.92	103	130	54.39	205
Eye pain	50	42.74	80	50	40.98	80	100	41.84	160
Visual acuity reduced	39	33.33	51	46	37.70	59	85	35.56	110
Conjunctival haemorrhage	39	33.33	44	41	33.61	47	80	33.47	91
Postoperative wound complication NOS	30	25.64	33	38	31.15	50	68	28.45	83
Conjunctival hyperaemia	37	31.62	44	28	22.95	38	65	27.20	82
Cataract NOS aggravated	23	19.66	33	29	23.77	35	52	21.76	68
Hypotony of eye	20	17.09	22	28	22.95	33	48	20.08	55
Eye irritation	21	17.95	27	25	20.49	38	46	19.25	65
Abnormal sensation in eye	20	17.09	26	26	21.31	35	46	19.25	61
Eye inflammation NOS	18	15.38	20	15	12.30	16	33	13.81	36
Vision blurred	15	12.82	19	17	13.93	21	32	13.39	40
Eye pruritus	13	11.11	18	18	14.75	20	31	12.97	38
Eyelid oedema	19	16.24	23	12	9.84	13	31	12.97	36
Vitreous haemorrhage	15	12.82	15	16	13.11	16	31	12.97	31
Cataract NOS	15	12.82	15	13	10.66	17	28	11.72	32
Postoperative complications NOS	14	11.97	16	13	10.66	16	27	11.30	32
Lacrimation increased	12	10.26	14	12	9.84	15	24	10.04	29
Maculopathy	12	10.26	14	13	10.66	13	25	10.46	27
Eye discharge	8	6.84	9	11	9.02	12	19	7.95	21
Vitreous floaters	10	8.55	12	9	7.38	10	19	7.95	22
Conjunctival oedema	6	5.13	7	9	7.38	9	15	6.28	16
Glaucoma NOS	7	5.98	8	8	6.56	10	15	6.28	18
Eyelid ptosis	6	5.13	7	7	5.74	7	13	5.44	14
Visual disturbance NOS	7	5.98	7	6	4.92	7	13	5.44	14
Postoperative wound site erythema	6	5.13	7	7	5.74	10	13	5.44	17
Ocular hyperaemia	7	5.98	7	5	4.10	6	12	5.02	13
Posterior capsule opacification	6	5.13	8	7	5.74	7	13	5.44	15
Choroidal detachment	4	3.42	4	7	5.74	8	11	4.60	12
Optic nerve cupping	3	2.56	3	8	6.56	8	11	4.50	11
Retinal detachment	6	5.13	6	3	2.45	3	9	3.77	9
Corneal oedema	6	5.13	8	2	1.64	3	8	3.35	11
<i>Fellow eye</i>									
Visual acuity reduced	17	14.53	19	19	15.57	21	36	15.06	40
Cataract NOS aggravated	18	15.38	20	14	11.48	19	32	13.39	39
Eye pain	10	8.55	11	14	11.48	16	24	10.04	27
Vision blurred	10	8.55	13	11	9.02	11	21	8.79	24
Vitreous floaters	8	6.84	8	13	10.66	15	21	8.79	23
Intraocular pressure increased	13	11.11	16	8	6.56	15	21	8.79	31
Conjunctival hyperaemia	8	6.84	9	5	4.10	6	13	5.44	15
Macular oedema	3	2.58	3	7	5.74	8	10	4.18	11
Iris adhesions	6	5.13	7	1	0.82	1	7	2.93	8

Source: Table 23 of sponsor's analysis

Table 26
Summary of key efficacy and safety parameters stratified by age-based
subgroups: Intent-to-Treat population
Study #BLP 415-001

	< 65 years			65 to < 75 years			≥75 years		
	N	Inci- dence	%	N	Inci- dence	%	N	Inci- dence	%
0.59 mg									
Study eyes									
Recur	106	12	11.3%	11	4	36.4%	---		
VA	105	62	59.0%	11	8	72.7%	---		
IOP	104	55	52.9%	11	4	36.4%	---		
Fellow eyes									
Recur	106	53	50.0%	11	4	36.4%	---		
VA	104	30	28.8%	11	4	36.4%	---		
IOP	103	8	7.80%	11	1	9.09%	---		
2.1 mg									
Study eyes									
Recur	118	11	9.32%	2	1	50.0%	2	0	0.00%
VA	117	61	52.1%	2	1	50.0%	2	1	50.0%
IOP	118	69	58.5%	2	1	50.0%	2	1	50.0%
Fellow eyes									
Recur	118	56	47.5%	2	1	50.0%	1	0	0.00%
VA	114	37	32.5%	2	0	0.00%	1	1	100%
IOP	115	10	8.70%	2	0	0.00%	1	0	0.00%

Source: Table 21 of Sponsor's analysis

Recur = Recurrence of uveitis; IOP = Elevation of IOP ≥ 10 mm Hg; VA = Worsening of visual acuity by 0.3 logMAR or greater

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Table 27
Summary of key efficacy and safety parameters stratified by Gender
subgroups: Intent-to-Treat population
Study #BLP 415-001

0.5 mg Dose	Male			Female		
	Total eyes	Inci- dence	%	Total eyes	Inci- dence	%
Study Recur	29	2	6.90%	81	5	6.17%
Study VA Increase >=0.3	29	14	48.2%	81	47	58.0%
Study IOP Increase >=10	29	20	69.0%	81	39	48.1%
Fellow Recur	28	14	50.0%	81	21	26.3%
Fellow VA Increase >=0.3	28	5	17.9%	81	15	18.5%
Fellow IOP Increase >=10	28	2	7.14%	81	7	8.64%

Source: Table 14.2.12.1.1 of sponsor's analysis

Table 27 (Continued)
Summary of key efficacy and safety parameters stratified by Gender
subgroups: Intent-to-Treat population
Study #BLP 415-001

2.0 mg Dose	Male			Female		
	Total eyes	Inci- dence	%	Total eyes	Inci- dence	%
Study Recur	48	4	8.33%	123	6	5.00%
Study VA Increase >=0.3	46	26	55.5%	113	69	58.0%
Study IOP Increase >=10	48	29	60.4%	123	75	62.5%
Fellow Recur	47	15	34.0%	123	55	45.8%
Fellow VA Increase >=0.3	46	7	15.2%	113	20	25.4%
Fellow IOP Increase >=10	47	6	12.8%	123	15	12.6%

Source: Table 14.2.12.1.1 of sponsor's analysis

Table 28
Summary of key efficacy and safety parameters stratified by Race
subgroups: Intent-to-Treat population
Study #BLP 415-001

Dose	Other			Caucasian			Black			Asian			Hispanic		
	Total eyes	Inci- dence	%												
Study Recur	3	0	0.00%	75	6	8.00%	19	1	5.26%	9	0	0.00%	4	0	0.00%
Study VA Increase- ≥0.3	3	2	66.7%	75	41	54.7%	19	10	52.6%	9	5	66.7%	4	2	50.0%
Study IOP Increase- ≥10	3	3	100%	75	41	54.7%	19	3	26.3%	9	7	77.8%	4	3	75.0%
Fellow Recur	3	0	0.00%	75	26	34.7%	13	9	47.4%	9	3	86.9%	2	2	56.7%
Fellow VA Increase- ≥0.3	3	2	66.7%	75	16	21.3%	13	0	0.00%	9	2	22.2%	2	0	0.00%
Fellow IOP Increase- ≥10	3	1	33.3%	75	3	4.00%	19	4	21.1%	9	0	0.00%	2	1	33.3%

Source: Table 14.2.12.8.1

Table 28 (Continued)
Summary of key efficacy and safety parameters stratified by Race
subgroups: Intent-to-Treat population
Study #BLP 415-001

Dose	Other			Caucasian			Black			Asian			Hispanic		
	Total eyes	Inci- dence	%												
Study Recur	4	0	0.00%	109	5	4.59%	30	4	13.3%	12	0	0.00%	13	0	7.69%
Study VA Increase- ≥0.3	4	2	50.0%	108	51	56.5%	30	16	53.3%	11	7	63.6%	12	9	75.0%
Study IOP Increase- ≥10	4	4	100%	109	60	57.8%	30	19	63.3%	12	10	83.3%	13	8	61.5%
Fellow Recur	4	3	75.0%	108	41	38.0%	30	15	50.0%	12	9	66.7%	13	4	30.8%
Fellow VA Increase- ≥0.3	4	0	0.00%	107	25	23.4%	30	5	16.7%	11	2	18.2%	12	5	41.7%
Fellow IOP Increase- ≥10	4	0	0.00%	108	11	10.2%	30	7	23.3%	12	3	25.0%	13	0	0.00%

Source: Table 14.2.12.8.1

Table 29
Summary of key efficacy and safety parameters stratified by Iris Color
subgroups: Intent-to-Treat population
Study #BLP 415-001

Dose	Brown			Blue			Hazel			Green			Other		
	Total eyes	Incidences	%												
Study Recur	62	2	3.23%	23	3	13.0%	16	2	12.5%	7	0	0.00%	2	0	0.00%
Study VA Increase- >=0.3	62	37	59.7%	23	12	52.2%	16	8	50.0%	7	4	57.1%	2	0	0.00%
Study IOP Increase- >=10	62	32	51.6%	23	14	60.9%	16	7	43.8%	7	5	71.4%	2	1	50.0%
Fellow Recur	61	21	34.4%	23	8	34.8%	16	4	25.0%	7	1	14.3%	2	1	50.0%
Fellow VA Increase- >=0.3	61	12	19.7%	23	4	17.4%	16	3	18.8%	7	1	14.3%	2	0	0.00%
Fellow IOP Increase- >=10	61	6	9.84%	23	1	4.35%	16	1	6.25%	7	1	14.3%	2	0	0.00%

Source: Table 14.2.12.7.1 of sponsor's analysis

Table 29 (Continued)
Summary of key efficacy and safety parameters stratified by Iris Color
subgroups: Intent-to-Treat population
Study #BLP 415-001

Dose	Brown			Blue			Hazel			Green			Other		
	Total eyes	Incidences	%												
Study Recur	96	8	8.33%	32	0	0.00%	27	1	3.70%	10	0	0.00%	3	1	33.3%
Study VA Increase- >=0.3	96	57	59.3%	32	17	53.1%	27	16	59.3%	10	3	30.0%	3	2	66.7%
Study IOP Increase- >=10	96	52	54.2%	32	19	59.4%	27	17	63.0%	10	5	50.0%	3	1	33.3%
Fellow Recur	96	45	46.9%	32	13	40.6%	26	7	26.9%	10	5	50.0%	3	1	33.3%
Fellow VA Increase- >=0.3	96	22	22.7%	32	6	18.8%	26	5	19.2%	10	2	20.0%	3	0	0.00%
Fellow IOP Increase- >=10	96	15	15.6%	32	3	9.38%	26	2	7.69%	10	1	10.0%	3	0	0.00%

Source: Table 14.2.12.7.1 of sponsor's analysis

Table 30
Summary of key efficacy and safety parameters stratified by age-based
subgroups: Intent-to-Treat population
Study #BLP 415-004

	< 65 years			65 to < 75 years			≥75 years		
	N	Inci- dence	%	N	Inci- dence	%	N	Inci- dence	%
0.59 mg									
Study eyes									
Recur	106	12	11.3%	11	4	36.4%	---		
VA	105	62	59.0%	11	8	72.7%	---		
IOP	104	55	52.9%	11	4	36.4%	---		
Fellow eyes									
Recur	106	53	50.0%	11	4	36.4%	---		
VA	104	30	28.8%	11	4	36.4%	---		
IOP	103	8	7.80%	11	1	9.09%	---		
2.1 mg									
Study eyes									
Recur	118	11	9.32%	2	1	50.0%	2	0	0.00%
VA	117	61	52.1%	2	1	50.0%	2	1	50.0%
IOP	118	69	58.5%	2	1	50.0%	2	1	50.0%
Fellow eyes									
Recur	118	56	47.5%	2	1	50.0%	1	0	0.00%
VA	114	37	32.5%	2	0	0.00%	1	1	100%
IOP	115	10	8.70%	2	0	0.00%	1	0	0.00%

Recur = Recurrence of uveitis; IOP = Elevation of IOP ≥ 10 mm Hg; VA = Worsening of visual acuity by 0.3 logMAR or greater

Source: Table 21 of sponsor's analysis

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Table 31
Summary of key efficacy and safety parameters stratified by Gender
subgroups: Intent-to-Treat population
Study #BLP 415-004

Dose	Female			Male		
	Total eyes	Incid- dence	%	Total eyes	Incid- dence	%
Study Recur	70	5	7.1%	47	11	23.4%
Study VA Increase- >=0.2	69	43	62.2%	47	27	57.4%
Study IOP Increase- >=10	65	31	47.6%	47	20	42.5%
Fellow Recur	70	34	48.6%	47	23	48.9%
Fellow VA Increase- >=0.2	69	10	14.5%	46	15	32.6%
Fellow IOP Increase- >=10	65	3	4.6%	46	6	13.0%

Source: Table 14.2.12.1.1 of sponsor's analysis

Table 31 (Continued)
Summary of key efficacy and safety parameters stratified by Gender
subgroups: Intent-to-Treat population
Study #BLP 415-004

Dose	Female			Male		
	Total eyes	Incid- dence	%	Total eyes	Incid- dence	%
Study Recur	64	3	4.69%	56	9	15.5%
Study VA Increase- >=0.2	63	25	41.3%	56	37	63.5%
Study IOP Increase- >=10	64	35	54.7%	56	26	46.4%
Fellow Recur	63	29	46.0%	56	20	35.7%
Fellow VA Increase- >=0.2	60	22	36.7%	57	16	28.1%
Fellow IOP Increase- >=10	61	2	3.28%	57	5	8.8%

Source: Table 14.2.12.1.1 of sponsor's analysis

Table 32
Summary of key efficacy and safety parameters stratified by Race
subgroups: Intent-to-Treat population
Study #BLP 415-004

Dose	Asian			Caucasian			Other			Black			Hispanic		
	Total eyes	Incidence	%												
Study Recur	83	14	16.8%	26	3	1.17%	5	0	0.00%	3	1	33.3%	2	0	0.00%
Study VA Increase >=0.3	83	48	57.8%	24	19	79.2%	5	5	100%	2	2	100%	2	1	50.0%
Study IOP Increase >=30	83	41	49.4%	28	18	64.3%	5	3	60.0%	2	1	50.0%	2	1	50.0%
Follow Recur	83	48	57.8%	24	16	66.7%	5	2	40.0%	3	2	66.7%	2	0	0.00%
Follow VA Increase >=0.3	83	28	33.7%	24	9	37.5%	5	1	20.0%	2	0	0.00%	2	1	50.0%
Follow IOP Increase >=30	83	9	10.8%	23	0	0.00%	4	0	0.00%	2	2	100%	2	0	0.00%

Source: Table 14.2.12.7.1

Table 32 (Continued)
Summary of key efficacy and safety parameters stratified by Race
subgroups: Intent-to-Treat population
Study #BLP 415-004

Dose	Asian			Caucasian			Other			Black			Hispanic		
	Total eyes	Incidence	%												
Study Recur	84	11	13.1%	25	3	1.17%	4	0	0.00%	4	0	0.00%	2	0	0.00%
Study VA Increase >=0.3	84	25	29.8%	27	14	51.9%	4	4	100%	4	4	100%	2	2	100%
Study IOP Increase >=30	84	46	54.8%	26	17	65.4%	4	3	75.0%	4	2	50.0%	2	2	100%
Follow Recur	84	44	52.4%	27	9	33.3%	4	1	25.0%	4	3	75.0%	2	0	0.00%
Follow VA Increase >=0.3	84	25	30.0%	26	5	19.2%	4	1	25.0%	4	2	50.0%	1	0	0.00%
Follow IOP Increase >=30	84	7	8.3%	27	2	7.4%	4	0	0.00%	4	0	0.00%	1	0	0.00%

Source: Table 14.2.12.7.1

Table 33
Summary of key efficacy and safety parameters stratified by Iris Color
subgroups: Intent-to-Treat population
Study #BLP 415-004

Dose	Less than 55			65 to under 75		
	Total eyes	Incid- [dence]	%	Total eyes	Incid- [dence]	%
Study Recur	105	12	11.8%	27	4	35.4%
Study VA Increase- ≥0.3	105	52	59.0%	27	5	72.7%
Study IOP Increase- ≥10	104	55	52.9%	27	4	35.4%
Fellow Recur	105	53	50.0%	27	4	35.4%
Fellow VA Increase- ≥0.3	104	39	25.8%	27	4	35.4%
Fellow IOP Increase- ≥10	105	5	7.77%	27	2	9.09%

Source: Table 14.2.12.5.1 of sponsor's analysis

Table 33 (Continued)
Summary of key efficacy and safety parameters stratified by Iris Color
subgroups: Intent-to-Treat population
Study #BLP 415-004

Dose	Less than 65			65 to under 75			75 and Older		
	Total eyes	Incid- [dence]	%	Total eyes	Incid- [dence]	%	Total eyes	Incid- [dence]	%
Study Recur	110	11	9.82%	2	1	50.0%	2	0	0.00%
Study VA Increase- ≥0.3	117	61	52.1%	2	1	50.0%	2	1	50.0%
Study IOP Increase- ≥10	116	69	59.3%	2	1	50.0%	2	1	50.0%
Fellow Recur	110	56	47.3%	2	1	50.0%	1	0	0.00%
Fellow VA Increase- ≥0.3	115	27	22.5%	2	0	0.00%	1	1	100%
Fellow IOP Increase- ≥10	115	10	8.70%	2	0	0.00%	1	0	0.00%

Source: Table 14.2.12.5.1 of sponsor's analysis

Table 34
Sub-Group Analysis of Uveitis Recurrence in Study Eye in Intent-to-treat patients
Study #BLP 415-001
(Reviewer's Table)

<i>Sub-group</i>	<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value¹</i>
Males	0.59 mg	29	11 (37.9%)	2 (6.9%)	0.0067
	2.1 mg	48	25 (52.1%)	5 (10.4%)	<0.0001
	Both doses	77	36 (46.8%)	7 (9.1%)	<0.0001
Females	0.59 mg	81	50 (61.7%)	4 (4.9%)	<0.0001
	2.1 mg	120	65 (54.2%)	5 (4.2%)	<0.0001
	Both doses	201	115 (57.2%)	9 (4.5%)	<0.0001
Age<65 Y	0.59 mg	97	52 (53.6%)	6 (6.2%)	<0.0001
	2.1 mg	155	83 (53.6%)	10 (6.5%)	<0.0001
	Both doses	252	135 (53.6%)	16 (6.3%)	<0.0001
65 Y≤Age<75 Y	0.59 mg	5	5 (100.6%)	0 (0.0%)	
	2.1 mg	12	6 (50.0%)	0 (0.0%)	
	Both doses	17	11 (64.7%)	0 (0.0%)	
Age≥75 Y	0.59 mg	8	4 (50.6%)	0 (0.0%)	
	2.1 mg	1	1 (100.0%)	0 (0.0%)	
	Both doses	9	5 (55.6%)	0 (0.0%)	
Caucasian	0.59 mg	75	45 (60.0%)	4 (5.3%)	<0.0001
	2.1 mg	109	63 (57.8%)	6 (5.5%)	<0.0001
	Both doses	184	108 (58.7%)	10 (5.4%)	<0.0001
Black	0.59 mg	19	9 (47.4%)	1 (5.3%)	0.0047
	2.1 mg	30	10 (33.3%)	3 (10.0%)	0.0348
	Both doses	49	19 (38.8%)	4 (8.2%)	0.0006
Asian	0.59 mg	9	3 (33.3%)	1 (11.1%)	0.3173
	2.1 mg	12	6 (50.0%)	0 (0.0%)	
	Both doses	21	9 (42.9%)	1 (4.8%)	0.0114
Hispanic	0.59 mg	4	3 (75.0%)	0 (0.0%)	
	2.1 mg	13	9 (69.2%)	1 (7.7%)	0.0047
	Both doses	17	12 (70.6%)	1 (5.9%)	0.0009
Other	0.59 mg	3	1 (33.3%)	0 (0.0%)	
	2.1 mg	4	2 (50.0%)	0 (0.0%)	
	Both doses	7	3 (42.9%)	0 (0.0%)	

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Table 34(Continued)
Sub-Group Analysis of Uveitis Recurrence in Study Eye in Intent-to-treat patients
Study #BLP 415-001
(Reviewer's Table)

<i>Sub-group</i>	<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value¹</i>
Blue Iris	0.59 mg	23	13 (56.5%)	2 (8.7%)	0.0009
	2.1 mg	32	15 (46.9%)	2 (6.2%)	0.0008
	Both doses	55	28 (50.9%)	4 (7.3%)	<0.0001
Brown Iris	0.59 mg	62	35 (56.5%)	3 (4.8%)	<0.0001
	2.1 mg	96	51 (53.1%)	6 (6.2%)	<0.0001
	Both doses	158	86 (54.4%)	9 (5.7%)	<0.0001
Green Iris	0.59 mg	7	3 (42.9%)	0 (0.0%)	
	2.1 mg	10	7 (70.0%)	0 (0.0%)	
	Both doses	17	10 (58.8%)	0 (0.0%)	
Hazel Iris	0.59 mg	15	9 (60.0%)	1(6.7%)	
	2.1 mg	27	15 (55.6%)	1(3.7%)	0.0002
	Both doses	42	24 (57.1%)	2 (4.8%)	<0.0001
Other Iris Color	0.59 mg	2	0 (0.0%)	0(0.0%)	
	2.1 mg	2	2 (100.0%)	1(50.0%)	
	Both doses	4	2 (50.0%)	1 (25.0%)	0.3173

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Table 35
Sub-Group Analysis of Uveitis Recurrence in Study Eye in Intent-to-treat patients
Study #BLP 415-004
(Reviewer's Table)

<i>Sub-group</i>	<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value¹</i>
Males	0.59 mg	47	11 (23.4%)	5 (10.6%)	0.0833
	2.1 mg	58	16 (27.6%)	8 (13.8%)	0.0593
	Both doses	105	27 (25.7%)	13 (12.4%)	0.0106
Females	0.59 mg	70	22 (31.4%)	5 (7.1%)	0.0011
	2.1 mg	64	20 (31.3%)	2 (3.1%)	0.0001
	Both doses	134	42 (31.3%)	7 (5.2%)	<0.0001
Age<65 Y	0.59 mg	106	33 (31.1%)	8 (7.6%)	<0.0001
	2.1 mg	118	33 (28.0%)	10 (8.5%)	0.0002
	Both doses	224	66 (29.5%)	18 (8.0%)	<0.0001
65 Y≤Age<75 Y	0.59 mg	11	0(0.0%)	2(18.2%)	
	2.1 mg	2	2(100.0%)	0 (0.0%)	
	Both doses	13	2 (15.4%)	2 (15.4%)	1.00
Age≥75 Y	0.59 mg	0	0 (0.0%)	0 (0.0%)	
	2.1 mg	2	1 (50.0%)	0 (0.0%)	
	Both doses	2	1 (50.0%)	0 (0.0%)	
Caucasian	0.59 mg	24	9 (37.5%)	1 (4.2%)	0.0114
	2.1 mg	28	12 (42.9%)	0 (0.0%)	
	Both doses	52	21 (40.4%)	1 (1.9%)	<0.0001
Black	0.59 mg	3	2 (66.7%)	0 (0.0%)	
	2.1 mg	4	3 (75.0%)	0 (0.0%)	
	Both doses	7	5 (71.4%)	0 (0.0%)	
Asian	0.59 mg	83	19 (22.9%)	9(10.8%)	0.0412
	2.1 mg	84	21 (25.0%)	10 (11.9%)	0.0278
	Both doses	167	40 (23.9%)	19 (11.4%)	0.0027
Hispanic	0.59 mg	2	2 (100.0%)	0(0.0%)	
	2.1 mg	2	0 (0.0%)	0(0.0%)	
	Both doses	4	2 (50.6%)	0 (0.0%)	
Other	0.59 mg	5	1 (20.0%)	0(0.0%)	
	2.1 mg	4	0 (0.0%)	0(0.0%)	
	Both doses	9	1 (11.1%)	0 (0.0%)	

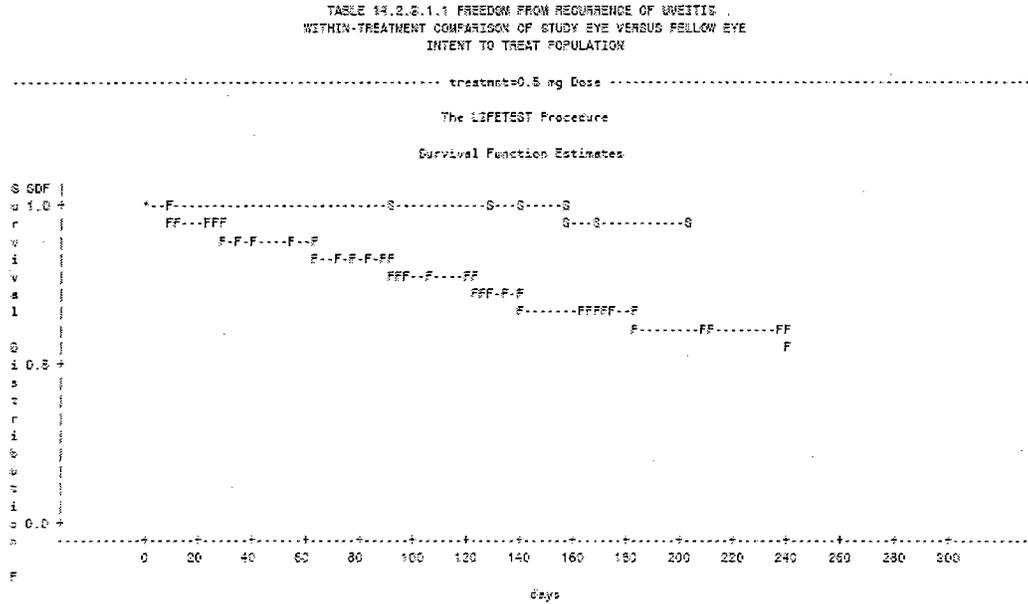
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Table 35 (Continued)
Sub-Group Analysis of Uveitis Recurrence in Study Eye in Intent-to-treat patients
Study #BLP 415-004
(Reviewer's Table)

<i>Sub-group</i>	<i>Dose</i>	<i>N</i>	<i>Pre-implant</i>	<i>Post-implant</i>	<i>P-value†</i>
Blue Iris	0.59 mg	11	4 (36.4%)	0 (0.0%)	
	2.1 mg	9	5 (55.6%)	0 (0.0%)	
	Both doses	20	9 (45.0%)	0 (0.09%)	
Brown Iris	0.59 mg	89	23 (25.8%)	9 (10.1%)	
	2.1 mg	91	22 (24.2%)	7 (7.7%)	0.0027
	Both doses	180	45 (25.0%)	16 (8.9%)	<0.0001
Green Iris	0.59 mg	2	1 (50.0%)	0 (0.0%)	
	2.1 mg	4	2 (50.0%)	0 (0.0%)	
	Both doses	6	3 (50.0%)	0 (0.0%)	
Hazel Iris	0.59 mg	3	2 (66.7%)	0 (0.0%)	
	2.1 mg	7	4 (57.1%)	0 (0.0%)	
	Both doses	10	6 (60.0%)	0 (0.0%)	

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Figure 1A
 Kaplan-Meier Plot for Risk of Responding on or Prior to The Week 34 Visit
 0.59 mg Treatment Group
 Study #BLP 415-001



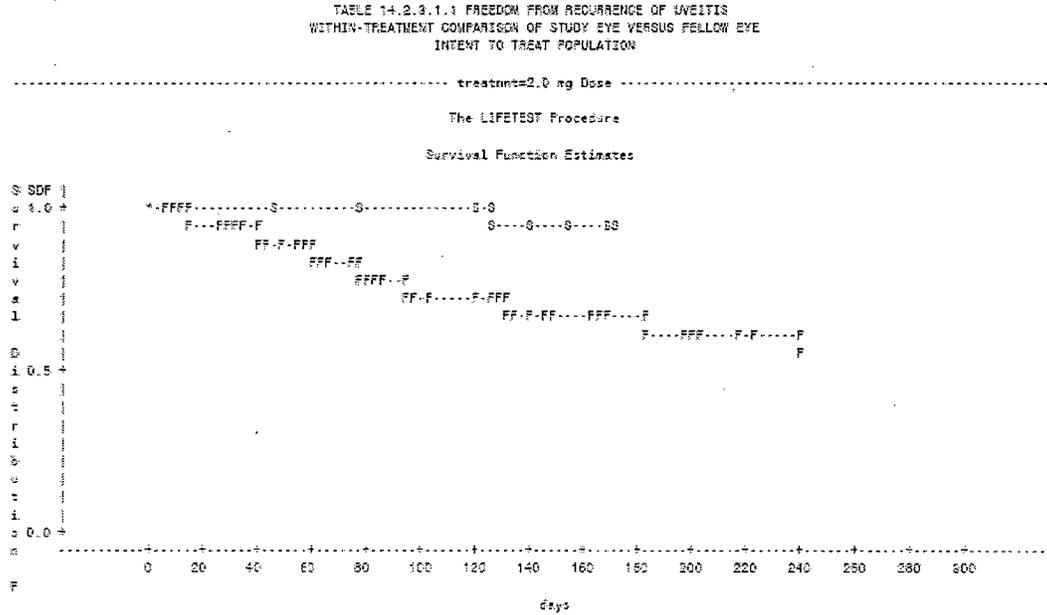
Kaplan-Meier plot for risk of responding on or prior to the Week 34 visit.
 Non-responders were censored at their last visit, or the date of the Week 34 visit, or Day 245 if the Week 34 visit were missed.

Source: Appendix 16.2.6
 Run on 30JUL04 at 12:12 from tablehead.res - Study #415-001

Symbols S= Study Eye and F= Fellow Eye

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Figure 1B
 Kaplan-Meier Plot for Risk of Responding on or Prior to The Week 34 Visit
 2.1 mg Treatment Group
 Study #BLP 415-001

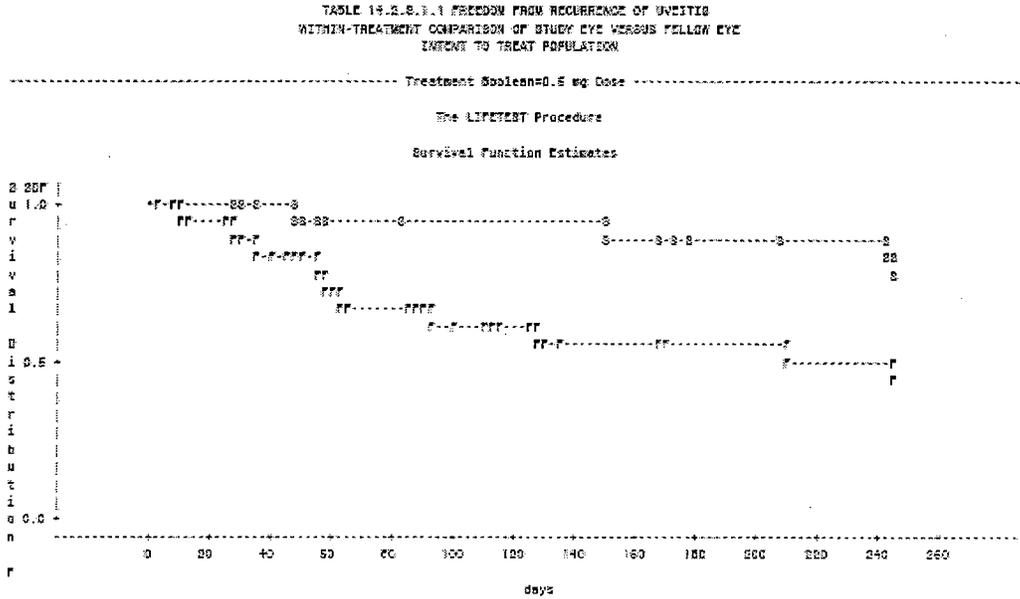


Kaplan-Meier plot for risk of responding on or prior to the Week 34 visit.
 Non-responders were censored at their last visit, or the date of the Week 34 visit, or Day 245 if the Week 34 visit were missed.
 Source: Appendix 16.2.5
 Run on 30JUL04 at 12:18 from tablehazard.ses - Study #415-001

Symbols S= Study Eye and F= Fellow Eye

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Figure 2A
 Kaplan-Meier Plot for Risk of Responding on or Prior to The Week 34 Visit
 0.59 mg Treatment Group
 Study #BLP 415-004

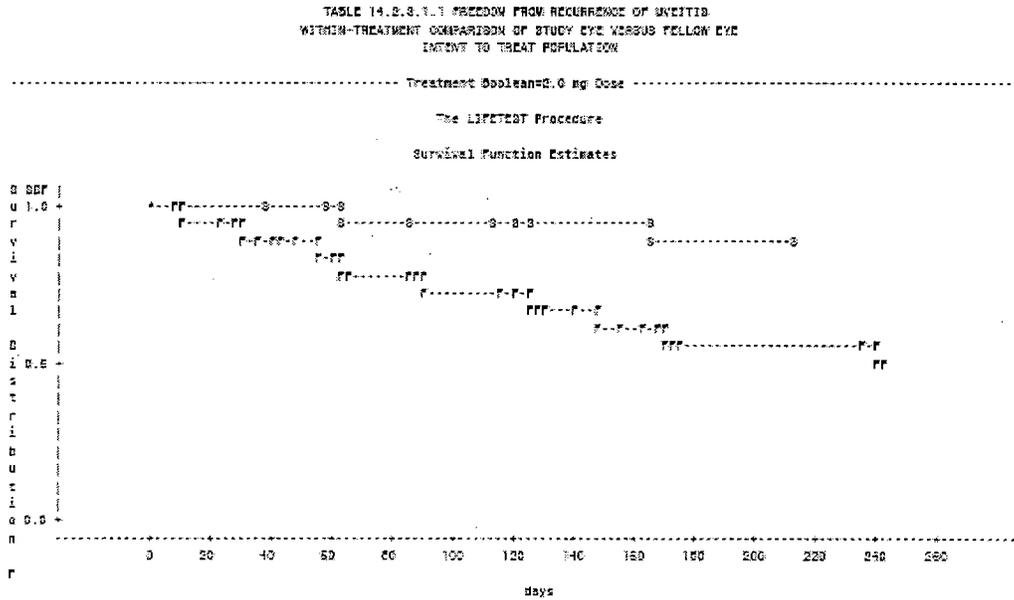


Kaplan-Meier plot for risk of responding on or prior to the Week 34 visit.
 Non-responders were censored at their last visit, or the date of the Week 34 visit, or Day 245 if the Week 34 visit were missed.
 Source: Appendix 16.2.8.3
 Run on 05AUG04 at 10:43 from tablehzard.123 - Study #915-004

Symbols S= Study Eye and F= Fellow Eye

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Figure 2B
 Kaplan-Meier Plot for Risk of Responding on or Prior to The Week 34 Visit
 2.1 mg Treatment Group
 Study #BLP 415-004



Kaplan-Meier plot for risk of responding on or prior to the Week 34 visit.
 Non-responders were censored at their last visit, on the date of the Week 34 visit, or Day 245 if the Week 34 visit were missed.
 Source: Appendix 16.2.6
 Run on 05AUG04 at 10:46 from tablehazard.sas - Study #415-004

Symbols S= Study Eye and F= Fellow Eye

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