CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

PRIMARY REVIEW

NDA #:	201923/45
Drug Name:	Iluvien, Fluocinolone Acetonide Intravitreal Insert 0.19mg
Indication:	Treatment of Diabetic Macular Edema
Applicant:	ALIMERA SCIENCES INC.
Date:	Stamp date: March 26, 2014
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Review Priority:	Priority
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Keywords: Best Corrected Visual Acuity, Intraocular Pressure, and Cataract Surgery.

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1 EXCUTIVE SUMMARY

Efficacy of ILUVIEN (0.2µg/day) for the treatment of diabetic macular edema was demonstrated in two phase 3, three-arm, Sham-controlled studies (Study A and Study B) based on statistically significant results for the primary efficacy endpoint of the proportion of subjects with a 15 letter or more gain from baseline evaluated at Month 24. Compared to Sham, approximately 12% [95% CI: (2.6%, 21.6%)] and 13% [95% CI: (2.6%, 23.2%)] more subjects in the ILUVIEN (0.2 µg/day) arm gained 15 letters or more in best-corrected visual acuity (BCVA) at Month 24 in Study A and Study B, respectively. Note that the treatment effect was not statistically significant at Month 36 in either of the two studies; however, the observed differences were numerically in favor of the ILUVIEN (0.2 µg/day) arm (Figure 1).

The analysis of the mean change from baseline in BCVA at months 24 (b) (4) the secondary efficacy endpoint, was supportive of the results of the dichotomous primary endpoint in Study B but not in Study A. In Study B, subjects in the ILUVIEN (0.2 µg/day) arm on average gained 5 [95% CI: (1, 9)] more letters in BCVA from baseline at Month 24 compared to Sham. There was however almost no difference between ILUVIEN (0.2 µg/day) and Sham in the mean change from baseline BCVA (b) (4) Month 24 (b) (4) in Study A (Figure 2).

One possible explanation for the relatively poor mean BCVA outcome in Study A is the confounding effect of treatment induced cataract formation that led to cataract surgery. In both studies, substantially large proportion of subjects in the ILUVIEN (0.2 µg/day) arm reported cataract formation and a significantly high proportion of them had cataract surgery (Table 7). To evaluate the possible confounding effect of cataract, subgroup analyses based on baseline lens and cataract surgery status were performed (Figure 5--Figure 7). In both studies, phakic subjects in the ILUVIEN (0.2 µg/day) arm exhibited a steep decline in BCVA starting from Month 6 up to around Month 18. This timeframe coincides with the time during which the majority of subjects had undergone cataract surgery (Table 9). On the other hand, pseudophakic subjects, who are not susceptible to cataract formation, showed an improved efficacy for ILUVIEN (0.2 µg/day) throughout the study course. Furthermore, among subjects who reported cataract formation, those who had cataract surgery during the study appeared to have better BCVA outcome compared to those who did not. Therefore, because subjects in both studies were mainly phakic and reported cataract formation and subsequently underwent cataract surgery, it is reasonable to assume that the decline in vision over time could be partly attributed to cataract formation and that cataract surgery might have reversed the decline to some degree.

Additional subgroup efficacy analyses conducted based on demographic and other baseline characteristics showed results that were consistent with the overall population. Of note were the subgroup of subjects with longer DME duration (more than the median duration of 1.73 years), which the applicant referred to as “Chronic DME”, and those with longer diabetic duration (>15 years). Subgroup of subjects in ILUVIEN (0.2 µg/day) arm with longer DME duration appeared to show a significantly improved efficacy both at Month 24 and Month 36 and a slightly better safety profile compared to other subgroups. A similarly improved efficacy was observed for subjects who had been diabetic for more than 15 years (Figure 9 and Figure 10).

Note that ILUVIEN (0.2 µg/day) is approved for the treatment of chronic DME in several European countries, and the applicant's proposed indication for this resubmission is (b) (4) [redacted] The efficacy summary over the course of the study by DME duration is presented in Figure 11. For subgroup of subjects with a DME duration of more than 1.73 years, the ILUVIEN (0.2 µg/day) arm had consistently higher proportion of subjects with a BCVA gain of at least 15 letters compared to Sham, with differences ranging between 11% to 27%. This result is supported by the result in the mean change from baseline BCVA over time. The ILUVIEN (0.2 µg/day) arm had consistently higher mean change from baseline BCVA compared to subjects in the Sham arm for the subgroup of subjects with longer DME duration (Figure 11). A similar efficacy pattern was observed for subjects with longer Diabetes duration (Figure 12).

With respect to safety, based on the three years data from the two studies combined, ILUVIEN (0.2 µg/day) treated subjects exhibited a significantly increased risk of cataract formation (subsequently leading to cataract surgery) and elevated intraocular pressure (IOP) in both studies. For phakic subjects, the net-risk of cataract formation was 31% [95% CI: (21%, 41%)] higher in the ILUVIEN (0.2 µg/day) arm compared to Sham; and the net-risk of cataract surgery was 53% [95% CI: (43%, 62%); Table 7] higher. For all subjects, the net-risk of elevated IOP adverse event was 25% [95% CI: (18%, 32%)] higher in the ILUVIEN (0.2 µg/day) arm compared to Sham (Table 7).

A risk-benefit analysis conducted on subjects who received at least one study treatment showed that, compared to Sham, a higher proportion of subjects in the ILUVIEN (0.2 µg/day) arm fell in the worst case scenario category, i.e., failed to achieve a 15 letter or more improvement in BCVA from baseline both at Month 24 and 36 but reported a treatment induced risk. At the Month 24 visit, 90 (24%) subjects in the ILUVIEN (0.2 µg/day) arm failed to achieve a 15 letter or more improvement in BCVA from baseline but reported at least one incidence of elevated IOP adverse event compared to 17 (9%) subjects in the Sham arm. On the other hand, slightly higher proportion of subjects in the ILUVIEN (0.2 µg/day) arm had the best case scenario of, i.e., a $\geq$15 letters improvement without reporting any IOP related AE compared to Sham arm [75 (20%) vs. 26 (15%)]. Similarly, a higher proportion of subjects in the ILUVIEN (0.2 µg/day) arm failed to achieve a 15 letters or more gain while needing cataract surgery, and lower proportion of subjects gained 15 letters or more from baseline without a need for cataract surgery (Figure 8). A similar pattern was observed at the Month 36 visit (Figure 15).

In summary, based on the totality of the efficacy findings, this reviewer concludes that there is evidence to support the efficacy of ILUVIEN (0.2 µg/day) for the treatment of DME provided that the observed treatment effect is deemed clinically meaningful and outweighs the safety risks of cataract surgery and elevated IOP.

Figure 1: Proportion of Subjects with a ≥15 Letters Gain from Baseline (ITT: LOCF)

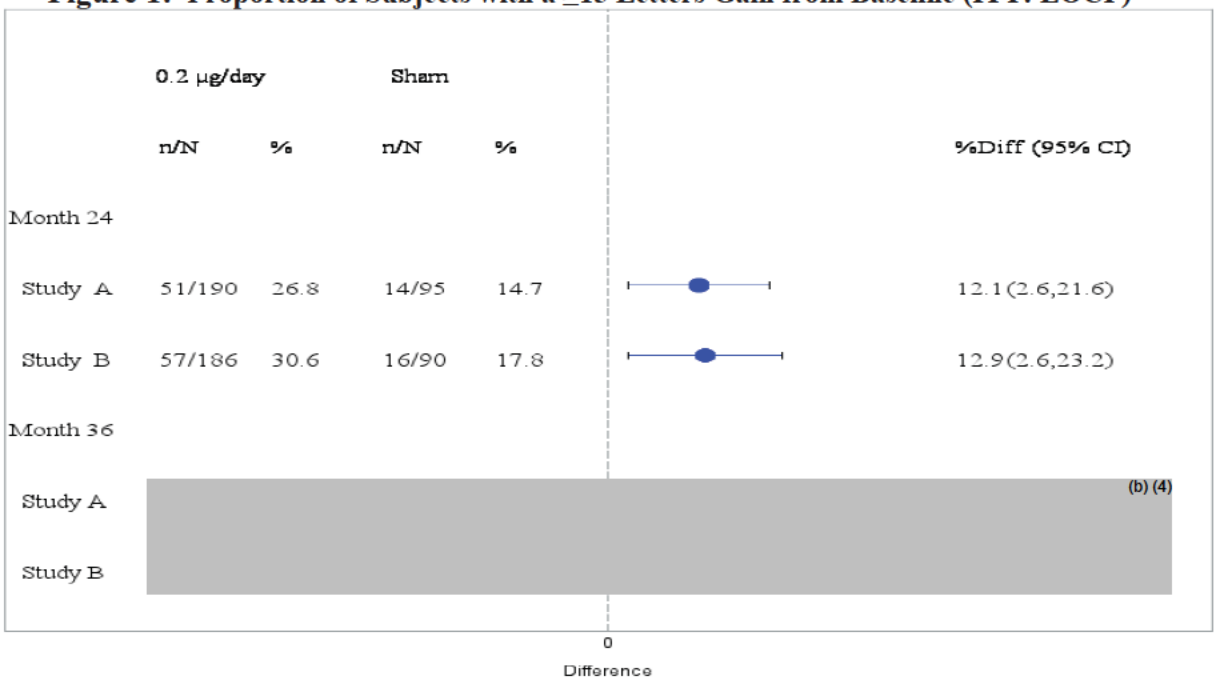
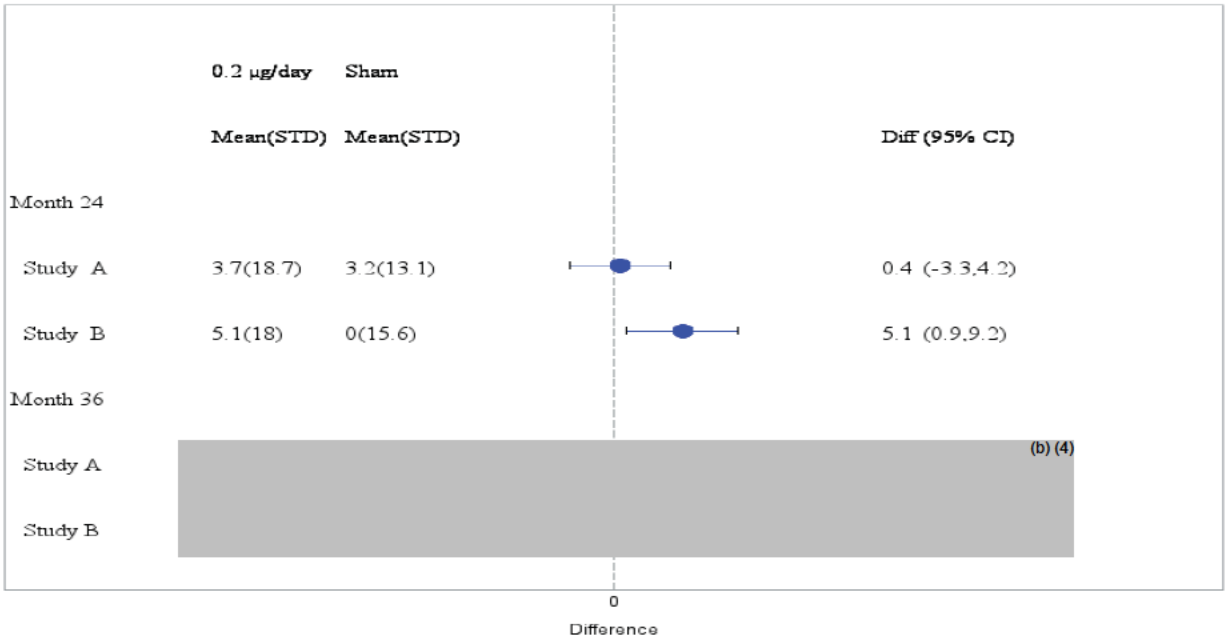


Figure 2: Mean change in BCVA from Baseline at Months 24 and 36 (ITT: LOCF)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

2 INTRODUCTION

Iluvien (fluocinilone acetonide intravitreal implant 0.19 mg) is a non-bioerodable, sustained release intravitreal insert which releases submicrogram levels of fluocinolone acetonide (FA) over (b) (4) 36 months with an initial release rate of (b) (4) µg/day. Two doses based on the initial release rate, 0.2 or 0.5 µg/day were evaluated in two phase 3 studies for the treatment of diabetic macular edema. The applicant sought approval for the low dose, 0.2 µg/day. A brief summary of the NDA submission history for this product is provided in the following table.

Table 1: Summary of Submission History

	Dates of Submission/ CR letter	Proposed indication	Clinical data	Some of the major deficiencies identified in clinical reviews
Original NDA (EDR link: \\CDSESUB1\evsprod\NDA201923\0000)	06/28/2010 12/22/2010	*treatment of diabetic macular edema*	24-month data of two on-going 36-month phase 3 studies	(1) There were significant risks of elevated IOP and cataract formation/surgery. (2) 36-month data were needed to further evaluate the potential benefits and risks of the test product
1st resubmission (EDR link: \\CDSESUB1\evsprod\NDA201923\0022)	05/12/2011 11/10/2011	(b) (4)	(1) 36-month data of two phase 3 studies (2) subgroup analysis by duration of DME (b) (4)	(1) There were significant risks of elevated IOP and cataract formation/surgery. (2) The observed benefit did not outweigh the risks.
2nd resubmission (EDR link: \\CDSESUB1\evsprod\NDA201923\0035)	04/26/2013 10/17/2013	(b) (4)	No new clinical data	Same as for the 1st resubmission.
3rd resubmission (current submission) (EDR link: \\CDSESUB1\evsprod\NDA201923\0045)	03/26/2014	(b) (4)	No new clinical data	

The current submission is the applicant's third resubmission for Iluvien. This resubmission seeks approval for Iluvien (b) (4) This resubmission does not include new efficacy and safety data.

Note that the original NDA was submitted to seek approval for Iluvien for *"the treatment of diabetic macular edema"* and included 24-month data from two ongoing 36-month phase 3 studies. The primary efficacy endpoint in the two phase 3 studies was the proportion of subjects with at least 15 letters gain from baseline at Month 24. The primary statistical reviews for the original NDA submission and the first re-submission were conducted by Dr. Rima Izem. In her original review, she concluded that the efficacy claim on BCVA at Month 24 is debatable. She argued that on the one hand the agency agrees with the applicant that the primary endpoint is met in both studies i.e. the treatment arms had higher proportion of subjects who gained 15 letters or more from baseline at 24 Month compared to the Sham arm. However, the treatment arms also had higher proportion of subjects who lost more than 15 letters from baseline at Month 24 compared to the Sham arm. Additionally, she indicated that three years data is needed to further evaluate the effect of cataract on BCVA. The agency also wrote the following comment in the CR letter sent to the applicant:

"The development of cataracts in eyes which were phakic at baseline creates difficulty in interpreting visual acuity during months 12 to 24. Due to the timing of the development of the cataracts and the time needed for postoperative recovery, 36-month clinical trial data will need to be evaluated to assess the potential benefits and risks associated with this drug product. Thirty-six month clinical trial data should be submitted to the application."

The applicant re-submitted the NDA with 36-month data and included analyses results for subgroup of subjects with DME duration (b) (4) The proposed indication in this submission was (b) (4) Following the review of the resubmission, the statistics review team deferred to the clinical team to weigh the benefit against the risk of the drug to the general population or in the subgroup of subjects with DME duration (b) (4) The clinical reviews stated that 36-month data suggested that the observed benefit did not outweigh the risks of the test product (for details, see Dr. Wiley Chambers's review posted in DARRTS on October 19, 2011). The agency issued a CR letter on November 10, 2011.

The applicant submitted a second resubmission in April 26, 2013. In this submission, the proposed indication was (b) (4) This submission did not include any new efficacy and safety data, but included applicant's justification why the observed benefit outweighed the risks of the test product for the limited indication. Again, the clinical reviews disagreed with the applicant's position on risk-benefit evaluation (for details, see Dr. Wiley Chambers's review posted in DARRTS on October 17, 2013). The agency sent another complete response letter to the applicant in October 17, 2013.

In a teleconference in November 2013 and a meeting that took place on December 13, 2013, the agency discussed with the applicant the possibility of limiting the indication (b) (4)

The applicant then submitted a third resubmission in March 2014 which included the efficacy and safety results for all subjects and subgroup of patients with DME duration of below and above the median (1.73 years) and a proposed indication (b) (4)

(b) (4) Note that in the previous submission, the applicant erroneously computed the median DME duration (b) (4)

The current review will be based on the NDA resubmission dated March 26, 2014 and will include the safety and efficacy analysis for all subjects and subgroups based on baseline demographic and other characteristics including subgroups formulated based on DME duration below and above the median (1.73 years). This review will therefore be used as an addendum to the previous reviews rather than replacing them.

3 Demographic and baseline characteristics and Patient Disposition

3.1 Demographic and Baseline characteristics

There were no significant baseline imbalances among the three arms in the demographics of age, gender, race or study eye iris color. In both studies, there were more male participants than female participants; and the majority of participants were white. The mean age of participants in Study A was slightly higher than those in Study B and the average DME duration was higher in subjects in Study A compared to B especially for Sham subjects (Table 2 and Table 3).

Table 2: Baseline and Demographics: Study A (ITT population)

	0.5 µg/day (N=196)	**0.2 µg/day (N=195)**	**Sham (N=95)**	**Total (N=494)**
Age(years)				
Mean (SD)	62.4(8.8)	64(9.6)	62.7(10.8)	63.1(9.5)
Median (Range)	62.9(35.5-84.1)	64.2(30.8-84.4)	62.4(32.6-85.8)	63.3(30.8-85.8)
<45	6(3.1%)	7(3.7%)	5(5.3%)	18(3.7%)
45-65	111(56.6%)	93(48.9%)	51(53.7%)	255(53%)
>65	79(40.3%)	90(47.4%)	39(41.1%)	208(43.2%)
Sex				
Male	118(60.2%)	110(57.9%)	48(50.5%)	276(57.4%)
Female	78(39.8%)	80(42.1%)	47(49.5%)	205(42.6%)
Race				
White	140(71.4%)	139(73.2%)	70(73.7%)	349(72.6%)
Black	12(6.1%)	11(5.8%)	6(6.3%)	29(6%)
Asian	43(21.9%)	39(20.5%)	19(20%)	101(21%)
Other	1(0.5%)	1(0.5%)	19(20%)	2(0.4%)
Iris Color				
Light	100(51%)	93(48.9%)	49(51.6%)	242(50.3%)
Dark	94(48%)	95(50%)	45(47.4%)	234(48.6%)
Baseline Lens Status				
Phakic	131(66.8%)	124(65.3%)	61(64.2%)	316(65.7%)
Pseudophakic	65(33.2%)	66(34.7%)	34(35.8%)	165(34.3%)
Diabetes Duration (Years)				
Mean (SD)	15.5(8.8)	16.3(10.2)	15.5(8.5)	15.8(9.3)
Median (Range)	15(1-39)	15(1-51)	15(1-42)	15(1-51)
DME Duration (Years)				
Mean (SD)	2.9(2.8)	2.9(3.4)	3.4(4.7)	3(3.5)
Median (Range)	2(0-14.4)	1.8(0-25)	2.1(0-36)	2(0-36)
HbA1c				
Mean (SD)	7.6(1.4)	7.6(1.5)	7.8(1.7)	7.6(1.5)
Median (Range)	7.3(4.8-13.5)	7.4(5.1-14.2)	7.5(5-13.8)	7.4(4.8-14.2)
Baseline BCVA				
Mean (SD)	52.5 (12.6)	53.4 (13.0)	54.8 (11.4)	53.3 (12.5)
Median (Range)	55 (20-71)	57 (19-75)	58 (25-69)	57 (19-75)

Source: Reviewer's Analysis

Table 3: Baseline and Demographics: Study B (ITT population)

	0.5 µg/day (N=199)	0.2 µg/day (N=186)	Sham (N=90)	Total (N=475)
Age(years)				
Mean (SD)	62.2(9.8)	61.8(9.1)	61.1(8.1)	61.8(9.2)
Range	62(20.5-86.6)	61.8(20.5-80)	61.5(39.6-83.2)	61.8(20.5-86.6)
<45	6(3%)	8(4.3%)	4(4.4%)	18(3.8%)
45-65	109(54.8%)	106(57%)	59(65.6%)	274(57.7%)
>65	84(42.2%)	72(38.7%)	27(30%)	183(38.5%)
Sex				
Male	127(63.8%)	105(56.5%)	60(66.7%)	292(61.5%)
Female	72(36.2%)	81(43.5%)	30(33.3%)	183(38.5%)
Race				
Caucasian	131(65.8%)	126(67.7%)	62(68.9%)	319(67.2%)
Black	20(10.1%)	11(5.9%)	5(5.6%)	36(7.6%)
Asian	44(22.1%)	46(24.7%)	21(23.3%)	111(23.4%)
Other	4(2%)	3(1.6%)	2(2.2%)	9(1.9%)
Iris Color				
Dark	128(64.3%)	127(68.3%)	58(64.4%)	313(65.9%)
Light	71(35.7%)	59(31.7%)	32(35.6%)	162(34.1%)
Baseline Lens Status				
Phakic	135(67.8%)	112(60.2%)	60(66.7%)	307(64.6%)
Pseudophakic	64(32.2%)	74(39.8%)	30(33.3%)	168(35.4%)
Diabetes Duration (Years)				
Mean (SD)	14.9(8.8)	15.7(8.5)	15.3(8.5)	15.3(8.6)
Median (Range)	14(0-55)	15(1-51)	15.5(1-37)	15(0-55)
DME Duration(Years)				
Mean (SD)	2.3(2.3)	2.3(2.3)	2.5(2.2)	2.3(2.3)
Median (Range)	1.5(0-12)	1.6(0-16)	2(0-11.1)	1.6(0-16)
HbA1c				
Mean (SD)	7.8(1.7)	8(1.6)	7.8(1.7)	7.9(1.6)
Median (Range)	7.5(4.7-14.1)	7.7(4.8-13.8)	7.4(5.4-15.3)	7.6(4.7-15.3)
Baseline BCVA				
Mean (SD)	53.3 (11.8)	53.3 (12.4)	54.7 (11.2)	53.6 (11.9)
Median (Range)	55 (19-68)	56 (20-70)	58 (21-68)	56 (19-70)

Source: Reviewer's Analysis

3.2 Subject Disposition

Slightly higher percentage of subjects in the two ILUVIEN arms completed the study compared to those in the Sham arm (Table **4**). The main reason for discontinuation was reported as subjects withdrawing consent (personal reason). A little over 7% and 6% of the study subjects in (ILUVIEN (0.5 µg/day) and ILUVIEN (0.2 µg/day)) arms and the Sham arm respectively died during the study.

Table 4: Patient Disposition

	0.5 µg/day	0.2 µg/day	Sham	Total
Study A				
Subjects Randomized	196 (100%)	190 (100%)	95 (100%)	481
Subjects Who completed the Study	132/196(67.3%)	141/190(74.2%)	67/95(70.5%)	
Subjects Who discontinued the Study	64/196(32.6%)	49/190(25.8%)	28/95(29.5%)	
Reason for Discontinuation				
Adverse Events	14/196(7.1%)	2/190(1.1%)	3/95(3.2%)	
Lack of Efficacy	1/196(0.5%)	0/190 (0.0%)	2/95(2.1%)	
Protocol Violations	3/196(1.5%)	2/190(1.1%)	2/95(2.1%)	
Personal Reason	13/196(6.6%)	19/190(10%)	6/95(6.3%)	
Lost-to-Follow-up	14/196(7.1%)	14/190(7.4%)	9/95(9.5%)	
Death	19/196(9.7%)	11/190(5.8%)	6/95(6.3%)	
Study B				
	0.5 µg/day	**0.2 µg/day**	**Sham**	**Total**
Subjects Randomized	199 (100%)	186 (100%)	90 (100%)	475
Subjects Who completed the Study	147/199(73.9%)	133/186(71.5%)	59/90(65.6%)	
Subjects Who discontinued the Study	52/199(26.1%)	53/186(28.5%)	31/90(34.4%)	
Reason for Discontinuation				
Adverse Events	1/199(0.5%)	2/186(1.1%)	2/90(2.2%)	
Lack of Efficacy	0/199 (0.0%)	0/186 (0.0%)	1/90(1.1%)	
Protocol Violations	2/199(1%)	0/186 (0.0%)	0/90 (0.0%)	
Personal Reason	14/199(7%)	12/186(6.5%)	8/90(8.9%)	
Lost-to-Follow-up	23/199(11.6%)	23/186(12.4%)	15/90(16.7%)	
Death	12/199(6%)	16/186(8.6%)	5/90(5.6%)	
Pooled				
	0.5 µg/day	**0.2 µg/day**	**Sham**	**Total**
Subjects Randomized	395 (100%)	376 (100%)	185 (100%)	956
Subjects Who completed the Study	279/395(70.6%)	274/376(72.9%)	126/185(68.1%)	
Subjects Who discontinued the Study	116/395(29.4%)	102/376(27.1%)	59/185(32.0%)	
Reason for Discontinuation				
Adverse Events	15/395(3.8%)	1/376(0.3%)	5/185(2.7%)	
Lack of Efficacy	1/395(0.3%)	4/376(1.1%)	3/185(1.6%)	
Protocol Violations	5/395(1.3%)	2/376(0.5%)	2/185(1.1%)	
Personal Reason	27/395(6.8%)	31/376(8.2%)	14/185(7.6%)	
Lost-to-Follow-up	37/395(9.4%)	37/376(9.8%)	24/185(13%)	
Death	31/395(7.8%)	27/376(7.2%)	11/185(5.9%)	

Source: Reviewer's Analysis.

The summary of subjects who had BCVA measures at each study visit and the number of subjects who remained in the study by visit are presented in Table 38 and Table 39 respectively. The number of subjects with observed BCVA measurements at Month 24 (not carried forward) was 144 (73.5%), 147 (77.4%) and 70 (73.7%) in the ILUVIEN (0.5 µg/day), ILUVIEN (0.2 µg/day) and Sham respectively for Study A, and 156 (78.4%), 140 (75.3%) and 64 (71.1%) in the ILUVIEN (0.5 µg/day), ILUVIEN (0.2 µg/day), and Sham respectively for Study B. Similarly, at Month 36, the number of subjects with observed BCVA measurements (not carried forward) was 132 (67.3%), 140 (73.7%) and 67 (70.5%) in the 0.5 µg/day, 0.2 µg/day and Sham respectively for Study A, and 144 (72.4%), 130 (69.9%) and 59 (65.6%) in the ILUVIEN (0.5 µg/day), ILUVIEN (0.2 µg/day), and Sham respectively for Study B.

4 Analysis Results

4.1 Study Design and Primary Endpoint

Study A and Study B were identical in design. They were multi-center, randomized, double-blind parallel-group studies, comparing the safety and efficacy of 0.2 μg/day and 0.5 μg/day fluocinolone acetonide intravitreal inserts to Sham injection in subjects with diabetic macular edema. Subjects were randomized into one of the three treatment arms in a 2:2:1 ratio. Only the study eye was treated with the assigned study drug and subjects were eligible for retreatment after Month 12 if they experienced vision loss (documented reductions of 5 or more letters) in visual acuity or thickening per optical coherence (minimum increase of 50 microns) as compared to subject's best status during the previous 12 months.

Efficacy outcome assessment visits occurred every 3 months starting from baseline until Month 36. The primary efficacy outcome was BCVA in the study eye and assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) method. The primary endpoint was the proportion of subjects with at least 15 letter gain from baseline at Month 24 with a final follow-up visit at Month 36. However, due to the fact that the majority of subjects in the study developed cataract and subsequently required surgery within the first few months of the study, there was potential difficulty in the interpretation of the primary endpoint at Month 24. The agency communicated this concern with the applicant and requested that efficacy results be evaluated at the Month 36 visit. In this review, efficacy and safety results both at Month 24 and Month 36 will be considered with more emphasis given to the Month 24 results as this is the time point the clinical team is basing their decision.

4.2 Statistical Analysis Methods

The primary efficacy analysis was performed on the full analysis set (ITT) which includes all randomized subjects. The between-treatment comparison was performed using the chi-square test, and the 95% CI for the treatment difference was calculated using the normal approximation for a binomial endpoint. Missing data were imputed using the last observation carried-forward (LOCF) method. In the analysis of mean BCVA change from baseline at each visit, treatment difference was tested using a t-test; and the 95% CI for the treatment difference was calculated using the normal approximation assuming unequal variances for treatment arms. To control the Type I error rate due to comparison of each dose against Sham, a Hochberg-Bonferroni correction was used.

The reviewer conducted risk-benefit analyses both at the subject and population levels. The subject level risk-benefit analysis first identified the risk-benefit outcome (four possible scenarios) for each individual subject and then calculated the proportion of subjects in each scenario for each treatment arm. The first scenario, referred to here as the best case scenario, is the case in which a pre-specified level of BCVA improvement was observed without incurring an AE. The worst case scenario is incurring an AE without achieving a pre-specified level of improvement in BCVA from baseline at Month 24 (Month 36). The other two scenarios are having benefit with AE, and no benefit and no AE. For the risk-benefit analysis at the population level, the unadjusted number needed to treat (NNT) and adverse event adjusted

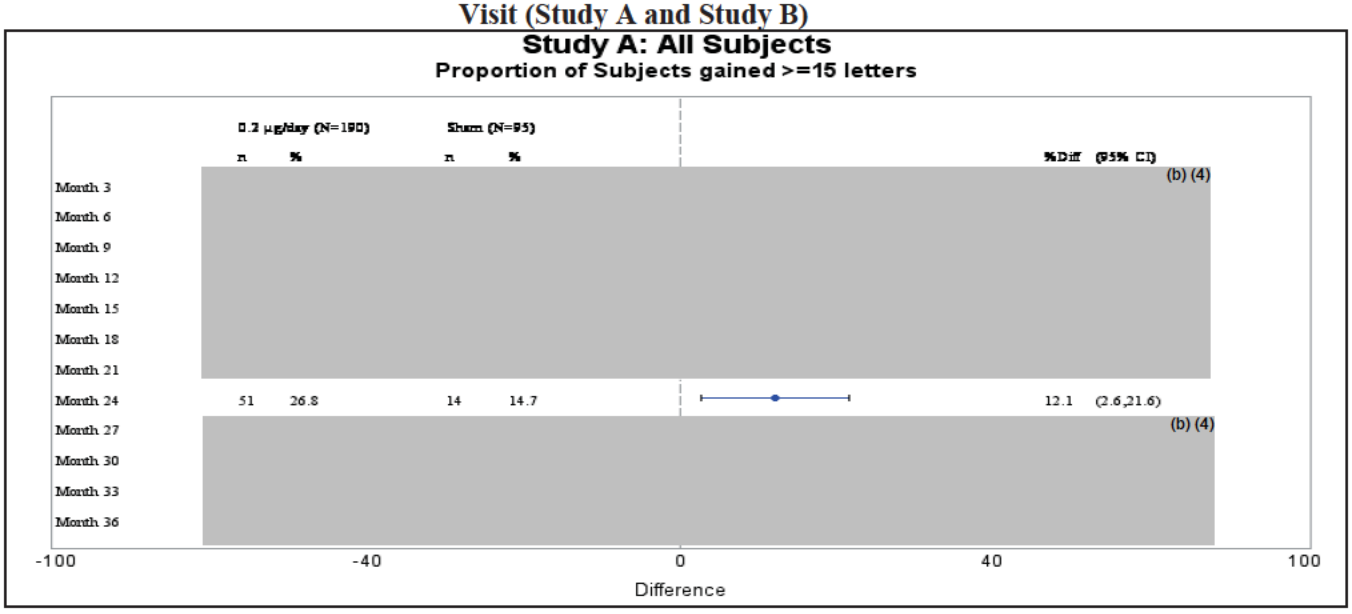
number needed to treat, Number Needed to Harm (NNH), together with the Benefit-Risk Ratio (BRR), the ratio of the NNH and NNT were computed for each benefit and risk combination.

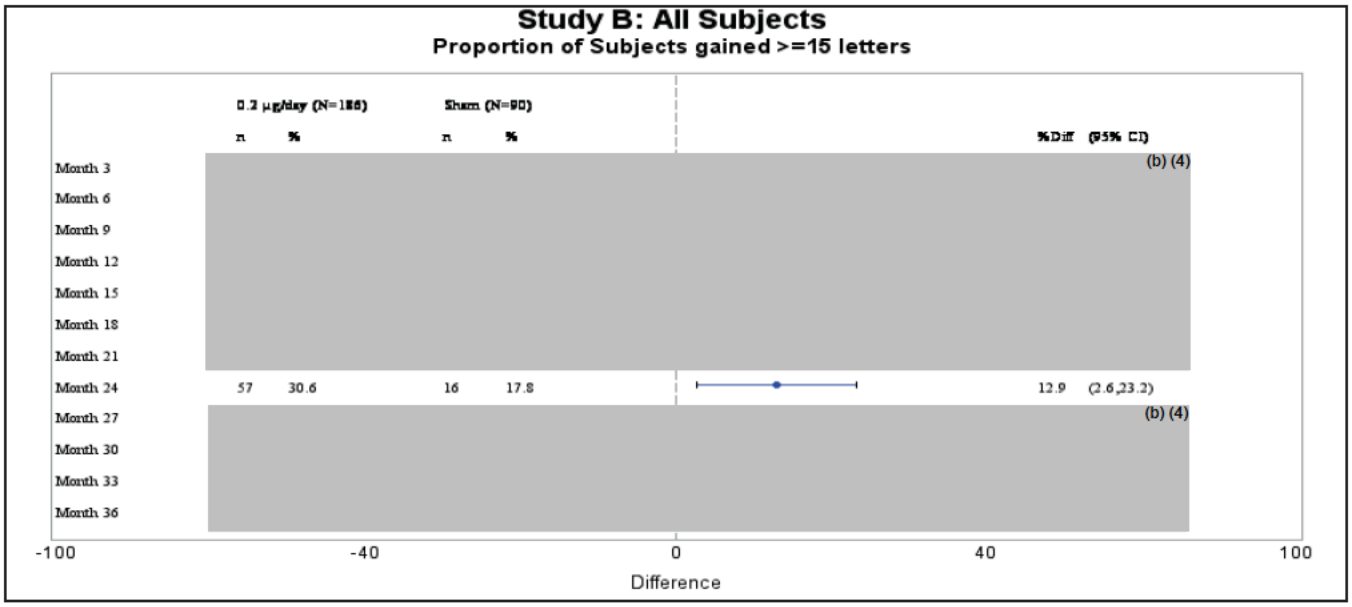
4.3 Primary Efficacy Results: Proportion of Subjects with BCVA Improvement ≥ 15 Letters

The results of the primary endpoint at Month 24 demonstrated evidence of efficacy in both studies. In Study A, approximately 27% and 15% subjects had BCVA improvements of ≥ 15 letters in the ILUVIEN (0.2 µg/day) and Sham arms, respectively; with a treatment difference of 12% [95% CI: (3%, 22%)]. In Study B, approximately 31% and 18% subjects had BCVA improvement of ≥15 letters in the ILUVIEN (0.2 µg/day) and Sham arms, respectively; with a treatment difference of 13% [95% CI: (3%, 23%)]. Compared with Month 24, however, the results at Month 36 were less favorable, showing a reduction in the treatment difference of approximately 3% in both studies. This decline resulted in a treatment difference at Month 36 which was not statistically significant. Note that, the reduced treatment difference at Month 36 seems mainly driven by an improved efficacy for subjects in the Sham arm rather than a substantial decline in efficacy of the ILUVIEN (0.2 µg/day) arm.

The effect of ILUVIEN (0.2 µg/day) appears to be consistent over the course of the study as can be seen in Figure 3. In both studies, the ILUVIEN (0.2 µg/day) arm had a higher proportion of subjects with BCVA improvement of ≥ 15 letters at all study visits compared to the Sham arm. In Study A, the treatment differences ranged from 4% to 12%, and were not statistically significant at visits between Month 9 and Month 21; and in Study B, the treatment differences were significant at all visits except at Months 3 and 36 and ranged between 6% and 18%.

Figure 3: Proportion of Subjects with BCVA Improvement ≥ 15 Letters from Baseline by Study Visit (Study A and Study B)





Source: Reviewer's Analysis. LOCF was used for imputing missing data.

4.4 Categorical Summary of BCVA change from baseline at Month 24 and 36

To have a detailed understanding of the treatment effect, additional summary of the proportion of subjects with different levels of gain and loss of vision at Month 24 and 36 was performed. In Study A, 26 (14%) subjects in the ILUVIEN (0.2 µg/day) arm lost BCVA by more than 15 letters from baseline at Month 24 compared to only 5 (5%) subjects in the Sham arm; and in Study B, the corresponding numbers were 22 (12%) and 9(10%), respectively. (b) (4)

Table 5: Categorical Summary of BCVA Change from Baseline at Month 24

BCVA Change	Study A			Study B		
	Treatment: N (%)			Treatment: N (%)		
	0.5 µg/day N=196	0.2 µg/day N=186	Sham N=95	0.5 µg/day N=199	0.2 µg/day N=186	Sham N=90
>=15 Letters Improvement	(b) (4)	51(26.8)	14(14.7)	(b) (4)	57(30.6)	16(17.8)
>=10 and <15 Letters Improvement		18(9.5)	13(13.7)		18(9.7)	6(6.7)
>=5 and <10 Letters Improvement		24(12.6)	14(14.7)		28(15.1)	11(12.2)
No Change (-5 to +5 Letters)		50(26.3)	34(35.8)		46(24.7)	25(27.8)
>=5 and <10 Letters Worsening		10(5.3)	9(9.5)		9(4.8)	13(14.4)
>=10 and <15 Letters Worsening		11(5.8)	6(6.3)		6(3.2)	10(11.1)
>=15 Letters Worsening		26(13.7)	5(5.3)		22(11.8)	9(10)

Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Table 6: Categorical Summary of BCVA Change from Baseline at Month (b) (4)

(b) (4)

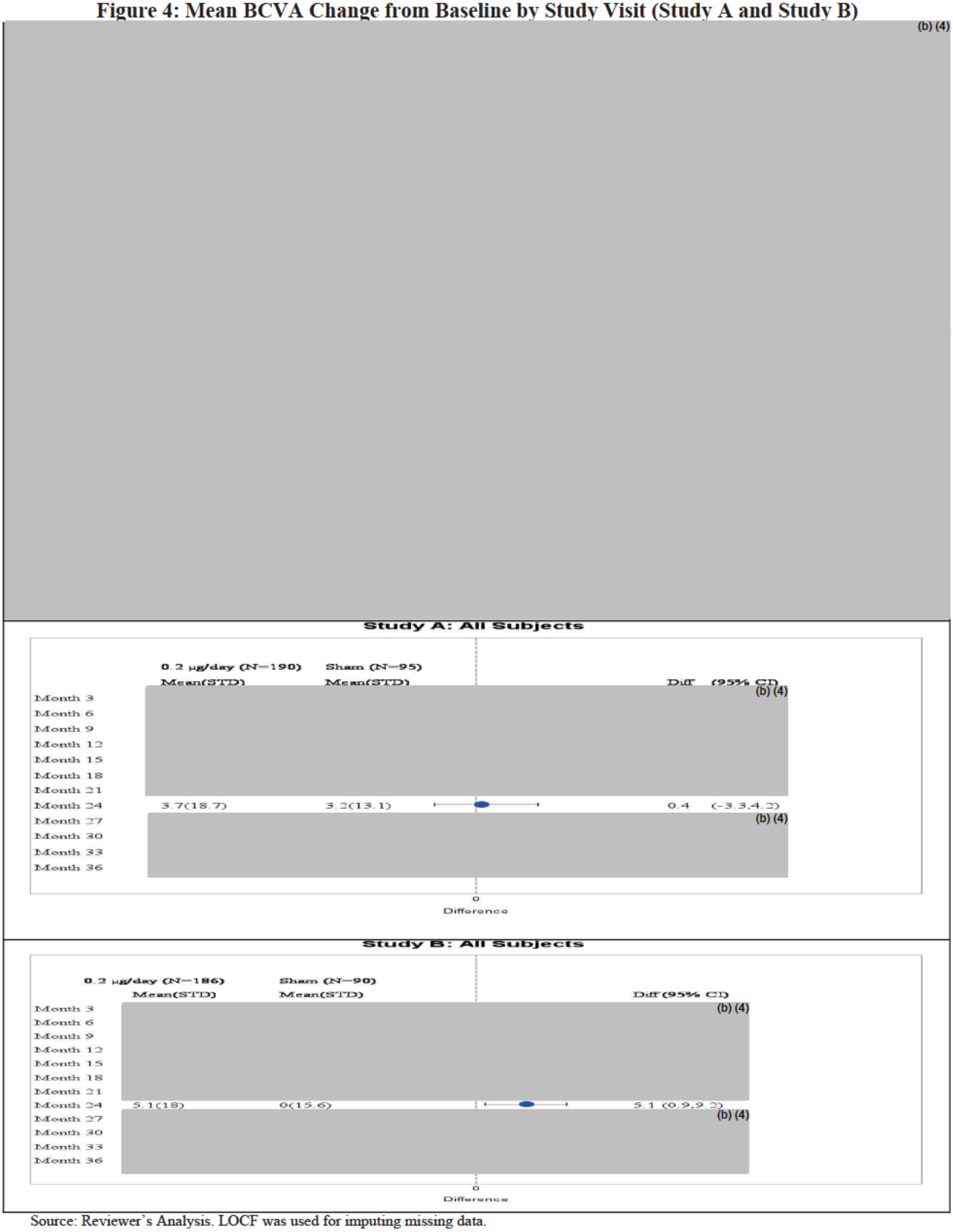
Source: Reviewer's Analysis. LOCF was used for imputing missing data.

4.5 Efficacy Results of Mean BCVA Change from Baseline

Mean BCVA changes from baseline at all post-baseline visits were considered as secondary efficacy endpoints. These endpoints take into account the magnitude of the BVCA values for all subjects and provide insight into whether, on average, subjects treated with ILUVIEN (0.2 µg/day) achieve more gain in vision improvement than subjects treated with Sham. The results of these endpoints are presented in Figure 4.

In Study A, the results of these endpoints were not supportive of the primary efficacy results. Although, compared to Sham, subjects in the ILUVIEN (0.2 µg/day) arm had numerically higher gains in BVCA at almost all visits; the treatment differences were statistically significant only at Months 3 and 6. The treatment difference at the Month 24 visit was 1 [95% CI: (-3, 4)] letter. These non-supportive results could be attributed to the confounding effect of cataract formation and the need for surgery in phakic subjects in the ILUVIEN (0.2 µg/day) (See Section 4.6 for details). In Study B, the results on the mean change from baseline BCVA were supportive of the results of the dichotomous endpoints. Subjects treated with ILUVIEN (0.2 µg/day) had consistently higher mean change from baseline values throughout the study period. The observed differences ranged between 3 and 7 letters and were statistically significant at all-time points except at Month 12.

Figure 4: Mean BCVA Change from Baseline by Study Visit (Study A and Study B)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

4.6 Confounding effect of cataract formation and cataract surgery

Steroid based treatments are known to induce cataract formation which leads to loss of vision over time. This is believed to have a confounding effect on the observed treatment effect. To evaluate the impact of treatment induced cataract formation on the BCVA over time, the graph of the mean BCVA change from baseline by baseline lens status is provided in Figure 5.

In both studies, phakic subjects in the ILUVIEN (0.2 µg/day) arm exhibited a steep decline in BCVA starting from Month 6 up to around Month 18. This timeframe coincides with the time during which the majority of subjects had undergone cataract surgery. Compared with Study B, cataracts appeared to cause vision loss at a much faster rate in Study A. It is also appears that in Study A, phakic subjects in the Sham arm had a better BCVA outcome compared to phakic Sham subjects in Study B. At Month 24, the net-gain in mean BCVA among phakic subjects was -1 [95% CI: (-6, 4)] letter in Study A and 3 [95% CI: (-2, 8)] letters in Study B. Similarly, at Month 36, a net-gain of 2 [95% CI: (-3, 7)] letters was seen in phakic subject in Study A, and 4 [95% CI: (-3, 7)] letters in Study B (Figure 7).

In both studies, pseudophakic subjects in the ILUVIEN (0.2 µg/day) arm had consistently higher mean change from baseline compared to subjects in the Sham arm throughout the study course. The treatment difference in mean BCVA change from baseline at Month 24 was 3 [95% CI: (-3, 10)] letters in Study A, and 8[95% CI: (1, 16)] letters in Study B (Figure 7).

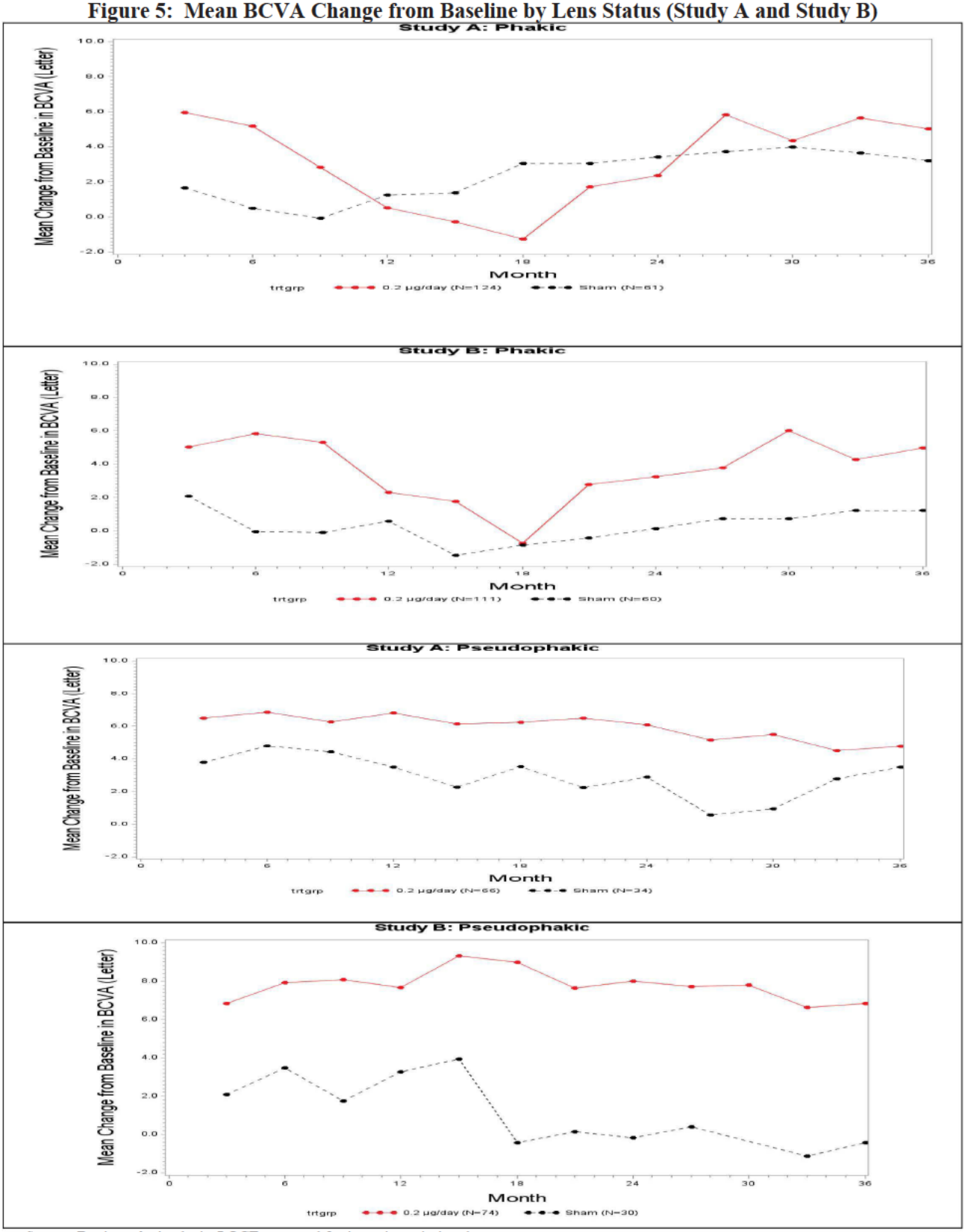
The mean plot of phakic subjects who reported cataract related AE from the two studies combined grouped into those who had surgery and those who did not is presented in Figure 6. In both arms, subjects who underwent cataract surgery seem to have re-gained their vision after the cataract surgery. There was a steady decline in vision for phakic subjects who reported cataract related adverse event but did not have cataract surgery during the study. Note that, a further classification of phakic subjects who reported cataract AE based on surgery status results in much small sample size in each subgroup. Thus results should be interpreted with caution. Additional detailed efficacy summaries by lens and cataract surgery status is provided in APPENDIX B.

The above summaries and those listed in APPENDIX B imply that subjects who developed cataract formation during the study had a decline in BCVA but seem to recuperate part of their vision with cataract surgery regardless of treatment. It is therefore possible to assume that cataract formation and subsequent surgery indeed played a confounding role in the evaluation of the treatment effect.

4.7 Efficacy Results of Mean Change from Baseline in Retinal Thickness

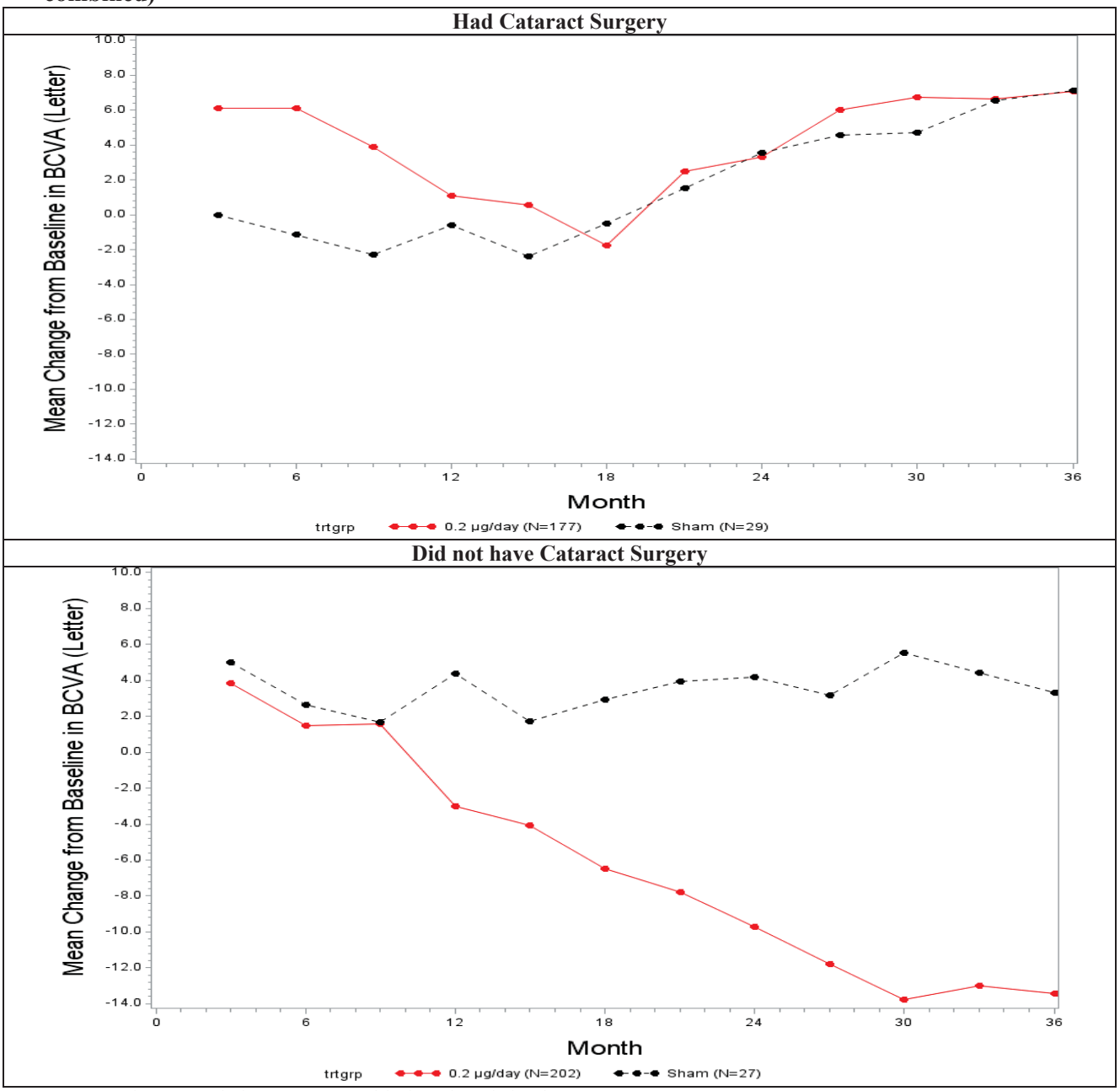
The mean change from baseline in retinal thickness was one of the secondary efficacy outcomes. The ILUVIEN (0.2 µg/day) arm had a consistently higher decline in retinal thickness from baseline at all study visits in both studies with differences ranging between -29 to -250 microns. Note however that the observed difference was significant at Month 24 in Study A only and at Month 36 in Study B only (Table 12).

Figure 5: Mean BCVA Change from Baseline by Lens Status (Study A and Study B)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

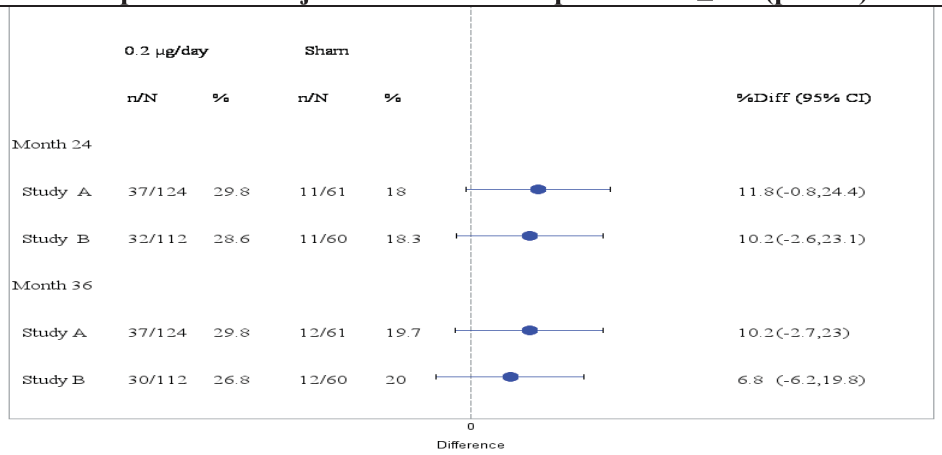
Figure 6: Mean BCVA Change from Baseline by Cataract Surgery Status (the two studies combined)



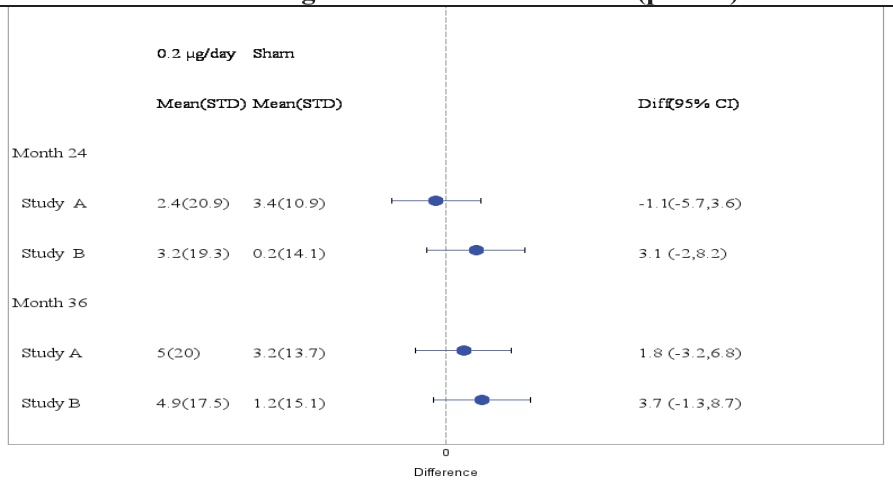
Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 7: Efficacy Results at Months 24 and 36 by lens status (Study A and Study B)

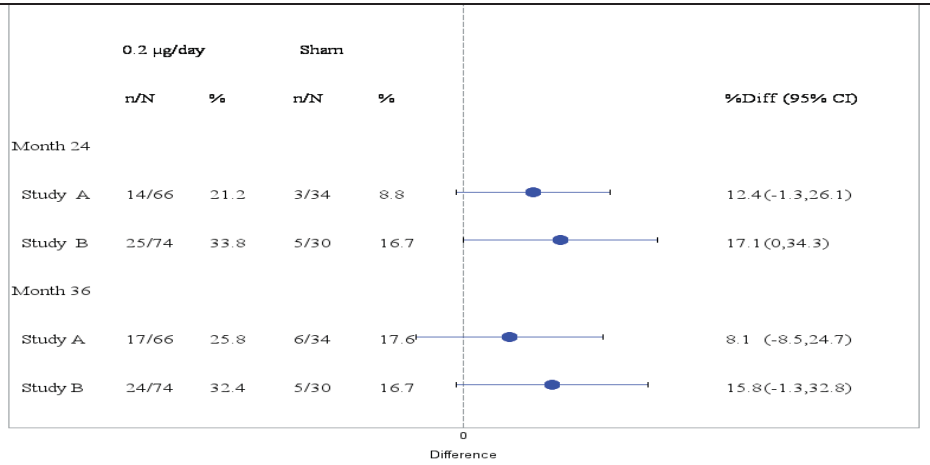
Proportion of Subjects with BCVA Improvement ≥ 15 (phakic)



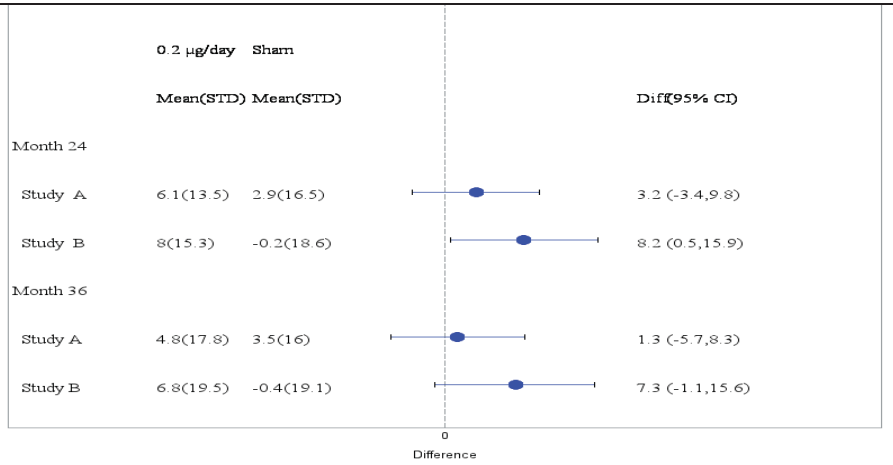
Mean Change in BCVA from baseline (phakic)



Proportion of Subjects with BCVA Improvement ≥ 15 (pseudophakic)



Mean Change in BCVA from baseline (pseudophakic)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

4.8 Safety Results

The two most frequently reported adverse events were cataract formation and elevated IOP related adverse events. By the end of the study (Month 36), compared to Sham, 32% (82% vs 50%) more ILUVIEN (0.2 µg/day) treated subjects reported at least one cataract related AE and 53% (80% vs 27%) more underwent cataract surgery, and 25% (37% vs. 12%) more had elevated IOP related adverse event (Table 7). Safety summary for each study separately and additional safety summaries for different groups are presented in Table 17--Table 29 in APPENDIX C.

Table 7: Summary of Adverse Events within three years (AE) (Pooled: All Treated Subjects)

	Treatment: N (%)			% Difference (95% CI)	
Adverse Events (AE)	**0.5 µg/day N=393**	**0.2 µg/day N=375**	**Sham N=185**	**0.5 µg/day vs. Sham**	**0.2 µg/day vs. Sham**
Any AE	389(99%)	369(98.4%)	175(94.6%)	4.4%(1%,7.8%)	3.8%(0.3%,7.3%)
Any Ocular AE	373(94.9%)	336(89.6%)	137(74.1%)	20.9%(14.2%,27.5%)	15.5%(8.5%,22.6%)
Any Serious AE	331(84.2%)	292(77.9%)	112(60.5%)	23.7%(15.8%,31.6%)	17.3%(9.1%,25.5%)
Any Ocular Serious AE	265(67.4%)	213(56.8%)	49(26.5%)	40.9%(33.1%,48.8%)	30.3%(22.2%,38.4%)
Any Severe AE	249(63.4%)	217(57.9%)	85(45.9%)	17.4%(8.8%,26%)	11.9%(3.2%,20.7%)
Any Ocular Severe AE	144(36.6%)	120(32%)	31(16.8%)	19.9%(12.7%,27.1%)	15.2%(8.1%,22.4%)
Any IOP Related AE	179(45.5%)	139(37.1%)	22(11.9%)	33.7%(26.9%,40.4%)	25.2%(18.4%,31.9%)
≥10 mm Hg IOP Change from Baseline at any visit	171(43.5%)	127(33.9%)	18(9.7%)	33.8%(27.3%,40.3%)	24.1%(17.7%,30.6%)
≥25 mm Hg IOP at any visit	176(44.8%)	133(35.5%)	23(12.4%)	32.4%(25.5%,39.2%)	23%(16.2%,29.8%)
≥30 mm Hg IOP at any visit	100(25.4%)	75(20%)	8(4.3%)	21.1%(15.9%,26.3%)	15.7%(10.7%,20.7%)
Glaucoma	18(4.6%)	19(5.1%)	4(2.2%)	2.4%(-0.5%,5.4%)	2.9%(-0.1%,6%)
IOP Lowering surgery	32(8.1%)	18(4.8%)	1(0.5%)	7.6%(4.7%,10.5%)	4.3%(1.9%,6.7%)
Any IOP Lowering Procedures	186(47.3%)	144(38.4%)	26(14.1%)	33.3%(26.2%,40.3%)	24.3%(17.3%,31.4%)
Trabeluctomy	22(5.6%)	10(2.7%)	0(0%)	5.6%(3.3%,7.9%)	2.7%(1%,4.3%)
Any Cataract Related AE Baseline Phakic Subjects	235(88.7%)	192(81.7%)	61(50.4%)	38.3%(28.6%,48%)	31.3%(21.1%,41.5%)
Cataract Surgery in Baseline Phakic Subjects	231(87.2%)	188(80%)	33(27.3%)	59.9%(51%,68.8%)	52.7%(43.3%,62.2%)
Death	31(7.9%)	28(7.5%)	11(5.9%)	1.9%(-2.4%,6.3%)	1.5%(-2.8%,5.8%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

In both studies, subjects in the ILUVIEN (0.2 µg/day) arm reported cataract formation for the first time and underwent cataract surgery much earlier than subjects treated with similar products such as Ozurdex (see Ozurdex labeling). The majority of subjects in all arms reported cataract formation and underwent cataract surgery within the first 18 months with some having surgery as early as 6 months (Table 8 and Table 9). The median times for cataract surgery were (15, 18, 15) months in the ILUVIEN (0.5 µg/day), ILUVIEN (0.2 µg/day) and Sham arms in Study A, and (18, 15, 18) months in n the ILUVIEN (0.5 µg/day), ILUVIEN (0.2 µg/day) and Sham arms in Study B (Table 9).

With respect to elevated IOP over time, The ILUVIEN (0.2 µg/day) arm had consistently higher mean IOP as can be seen in Figure 14.

Table 8: Summary of Time-to-Cataract AE among Baseline Phakic Subjects

Time to First Cataract Related AE (Month)	Study A			Study B		
	0.5 µg/day N=130	0.2 µg/day N=124	Sham N=61	0.5 µg/day N=135	0.2 µg/day N=111	Sham N=60
≤Month 6	30(23.1%)	24(19.4%)	9(14.8%)	34(25.2%)	23(20.7%)	9(15%)
> Month 6 ≤ Month 12	48(36.9%)	37(29.8%)	9(14.8%)	47(34.8%)	29(26.1%)	8(13.3%)
Month 15	20(15.4%)	17(13.7%)	2(3.3%)	20(14.8%)	16(14.4%)	1(1.7%)
Month 18	11(8.5%)	11(8.9%)	4(6.6%)	12(8.9%)	9(8.1%)	3(5%)
Month 21	4(3.1%)	6(4.8%)	3(4.9%)	4(3%)	5(4.5%)	2(3.3%)
Month 24	2(1.5%)	6(4.8%)	0 (0.0%)	3(2.2%)	4(3.6%)	2(3.3%)
Month 27	0 (0.0%)	1(0.8%)	2(3.3%)	0 (0.0%)	0 (0.0%)	1(1.7%)
Month 30	0 (0.0%)	0 (0.0%)	2(3.3%)	0 (0.0%)	4(3.6%)	1(1.7%)
Month 33	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1(1.7%)
Month 36	0 (0.0%)	0 (0.0%)	2(3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mean (STD) Median Q1, Q3	11 (5) 12 6, 15	12 (6) 11 9, 15	14 (10) 12 6, 21	11 (6) 12 6, 15	12 (7) 12 6, 15	13 (9) 9 6, 20

Source: Reviewer's analysis.

Table 9: Summary of Time-to-Cataract Surgery among Baseline Phakic Subjects

Time to First Cataract surgery (Month)	Study A			Study B		
	0.5 µg/day N=130	0.2 µg/day N=124	Sham N=61	0.5 µg/day N=135	0.2 µg/day N=111	Sham N=60
≤Month 6	9(6.9%)	7(5.6%)	4(6.6%)	9(6.7%)	5(4.5%)	4(6.7%)
> Month 6 ≤ Month 12	31(23.8%)	25(20.2%)	3(4.9%)	26(19.3%)	19(17.1%)	2(3.3%)
Month 15	21(16.2%)	17(13.7%)	2(3.3%)	22(16.3%)	19(17.1%)	2(3.3%)
Month 18	25(19.2%)	19(15.3%)	1(1.6%)	27(20%)	16(14.4%)	3(5%)
Month 21	15(11.5%)	16(12.9%)	2(3.3%)	24(17.8%)	10(9%)	1(1.7%)
Month 24	5(3.8%)	11(8.9%)	2(3.3%)	6(4.4%)	5(4.5%)	2(3.3%)
Month 27	4(3.1%)	4(3.2%)	0(0.0%)	2(1.5%)	5(4.5%)	3(5%)
Month 30	1(0.8%)	4(3.2%)	0(0.0%)	3(2.2%)	4(3.6%)	1(1.7%)
Month 33	0(0.0%)	0(0.0%)	0(0.0%)	1(0.7%)	2(1.8%)	0(0.0%)
Month 36	0(0.0%)	0(0.0%)	1(1.6%)	0(0.0%)	0(0.0%)	0(0.0%)
Mean (STD) Median Range	16 (6) 15 12, 18	16 (6) 18 12, 21	15 (9) 15 6, 21	16 (6) 18 12, 21	17 (7) 15 12, 21	17 (9) 18 9, 24

Source: Reviewer's analysis.

4.9 Risk benefit analysis results

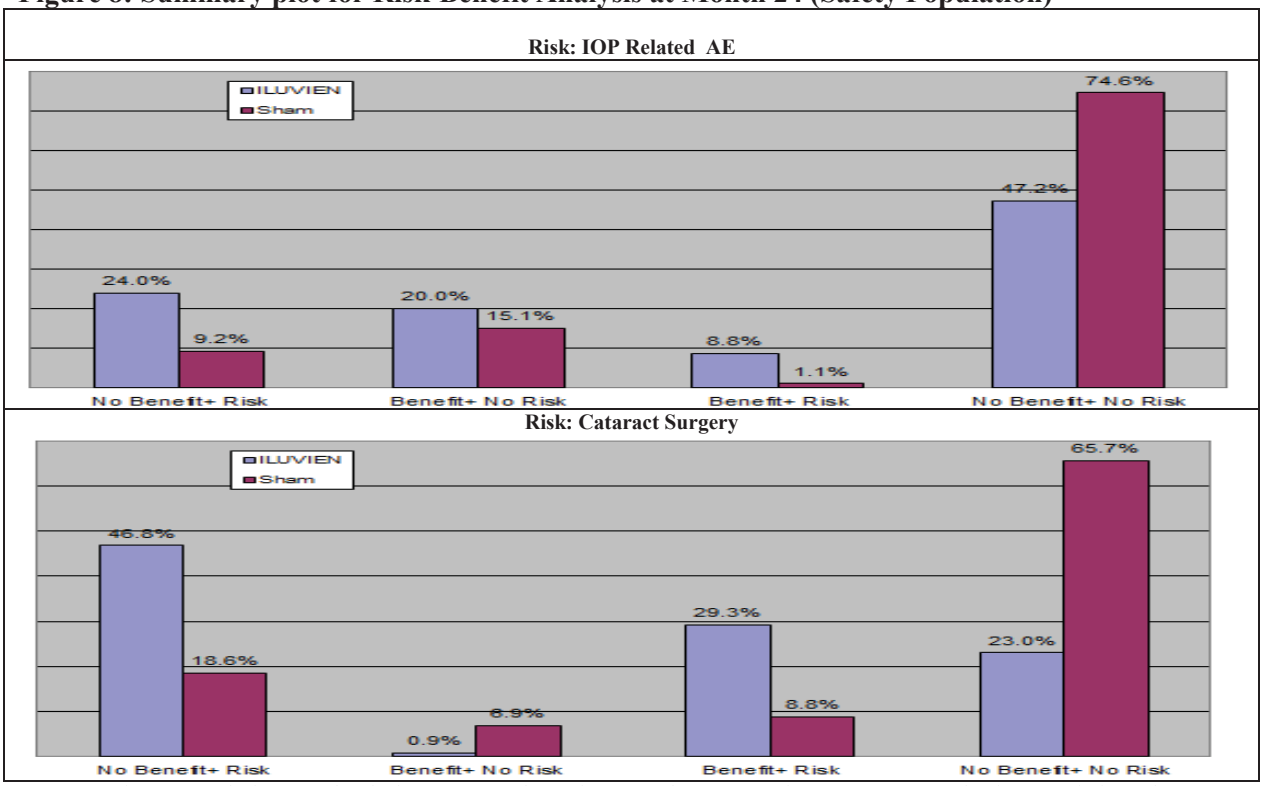
Compared to Sham, at the Month 24 risk-benefit evaluation, the ILUVIEN (0.2 µg/day) arm had a higher proportion of subjects with the worst case scenario, and lower or only slightly higher proportion of subjects with the best case scenario for the majority of risks considered. Additionally, the ILUVIEN (0.2 µg/day) arm also had a higher proportion of subjects who achieved improvement in BCVA but incurred an AE and lower proportion of subjects with no benefit and no AE compared to Sham (Table 32).

A higher proportion of subjects in the ILUVIEN (0.2 µg/day) arm failed to achieve a 15 letter or more improvement in BCVA from baseline at Month 24 but reported at least one IOP related AE (Worst Case Scenario) compared to subjects in the Sham arm (90 (24%) vs. 17 (9.2%). Slightly higher proportion of subjects in the ILUVIEN (0.2 µg/day) arm had the best case scenario i.e., ≥15 letters improvement without reporting any IOP related AE [75 (20%) vs. 28 (15%) at Month 24; Figure 8].

For baseline phakic subjects, more subjects underwent cataract surgery but failed to achieve a 15 letter or more BCVA improvement from baseline at Month 24 (Worst Case Scenario) in the ILUVIEN (0.2 µg/day) arm compared to Sham (104 (47%) vs. 19 (19%)). The proportion of baseline phakic subjects with a 15 letter or more BCVA improvement from baseline at Month 24 without requiring cataract surgery (Best Case Scenario) however was 6% lower in the ILUVIEN (0.2 µg/day) arm compared to Sham (2 (1%) vs. 7 (7%)) (Figure 8).

For the majority of risks considered, the Benefit-to-Risk Ratios (BRR) were less than one or equivalently the Number NNT was larger than the NNH. The BRR values of 0.56 and 0.3 corresponding to Any IOP related AE and Cataract Surgery for phakic subjects imply that for every subject with a 15 letter or more BCVA improvement due to ILUVIEN (0.2 µg/day), approximately 2 subjects had at least one IOP related AE and approximately 3 phakic subjects required cataract surgery, respectively.

Figure 8: Summary plot for Risk-Benefit Analysis at Month 24 (Safety Population)



Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension). LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Both risk and benefit were evaluated at Month 24. ILUVIEN refers to the ILUVIEN (0.2 µg/day) arm.

4.10 Subgroup analysis results

The summary results for the comparison of the ILUVIEN (0.2 µg/day) arm and Sham with respect to the proportion of subjects with a 15 letter or more gain from baseline at Month 24 and the mean change from baseline BCVA for subgroup of subjects are summarized in Figure 9 and Figure 10. The conclusions for the subgroup analyses are based on the pooled data from the two Phase 3 studies. The subgroup analysis results presented in this section are considered descriptive and should only be used to characterize the observed treatment differences between subgroups. Unless stated otherwise, all analyses are performed on the ITT population with LOCF used to impute missing data.

Overall, the subgroup analysis results based on baseline demographics were consistent with the primary efficacy analysis results. Additional subgroup analyses for subgroups formed based on duration of diabetes (≤ 15 years versus > 15 years), duration of DME (≤ 1.73 years versus > 1.73 years), baseline HbA1c (≤ 8% versus > 8%), and lens status at baseline (phakic study eye versus pseudophakic study eye) was conducted.

Of all the subgroup analyses results, the analysis results of the subgroup based on diabetic duration (> 15 years) and DME duration (≥ 1.73 years) stood out. The subgroup of subjects with DME duration greater than 1.73 years was selected by the applicant as the target subgroup for the treatment. It is observed that subjects in the ILUVIEN (0.2 µg/day) arm with longer DME duration, defined as a DME duration greater than the median DME duration for the overall population (1.73 years), had a very significant efficacy both at Month 24 and Month 36 and a slightly better safety profile. The applicant refers to this subgroup of subjects as "Chronic DME". A similarly improved efficacy was observed for subjects who had been diabetic for more than 15 years. Note that ILUVIEN (0.2 µg/day) is approved for the treatment of chronic DME in several European countries.

The proportion of subjects with a gain of at least 15 letters from baseline and the mean BCVA change from baseline at all study visits by the duration of DME is presented in Figure 11. The ILUVIEN (0.2 µg/day) arm had consistently higher proportion of subjects with a BCVA gain of at least 15 letters compared to Sham for subjects with longer DME duration, with differences ranging between 11% to 27%. This result is further emphasized in the mean change from baseline BCVA over time. The ILUVIEN (0.2 µg/day) arm had consistently higher mean change from baseline BCVA compared to subjects in the Sham arm for the subgroup of subjects with longer DME duration. A similar efficacy pattern was observed for subjects with longer Diabetes duration (Figure 12).

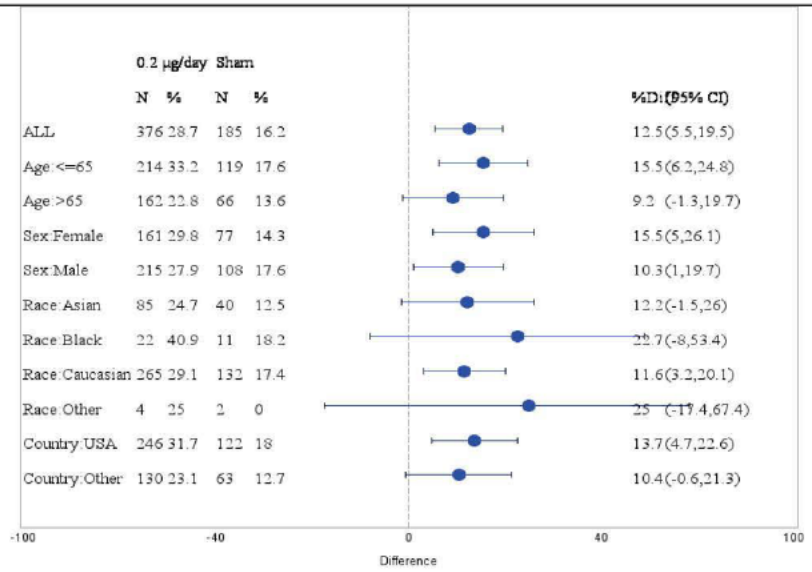
Figure 9: Subgroup Analysis: Proportion of Subjects with a 15 Letter or more Gain from Baseline

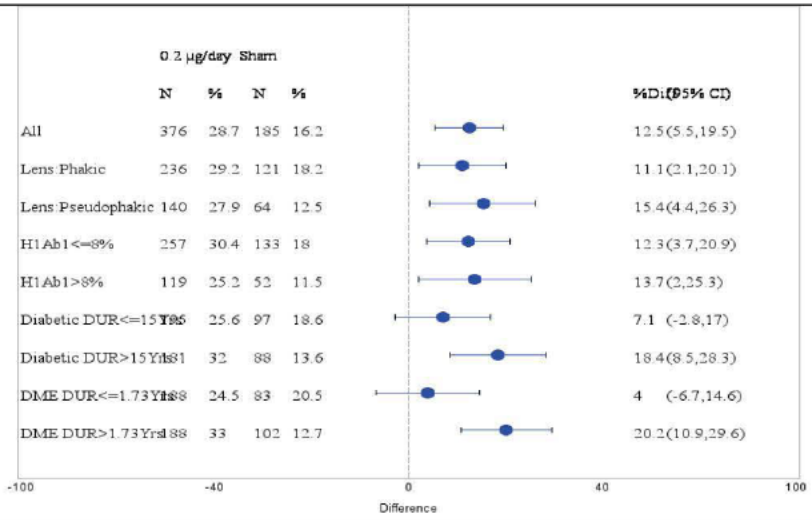
(b) (4)

Month 24

Month

(b) (4)



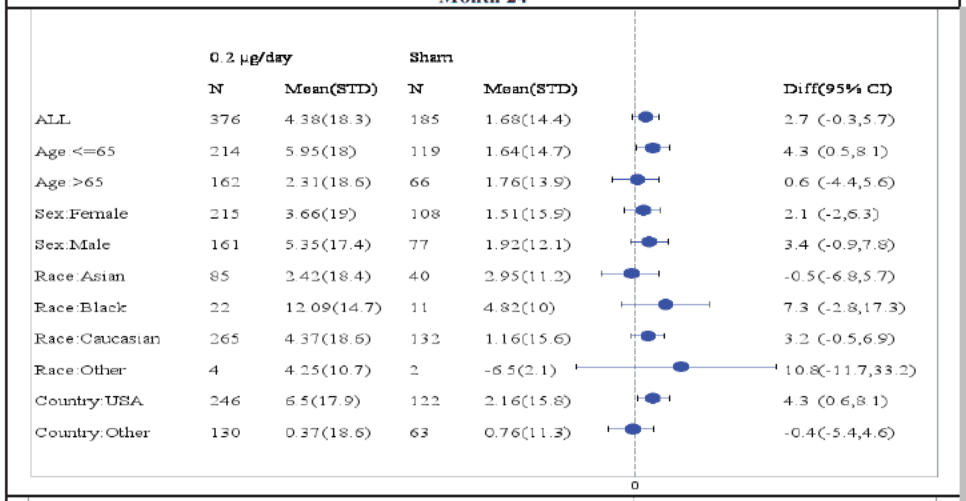


Source: Reviewer's Analysis. LOCF was used for imputing missing data.

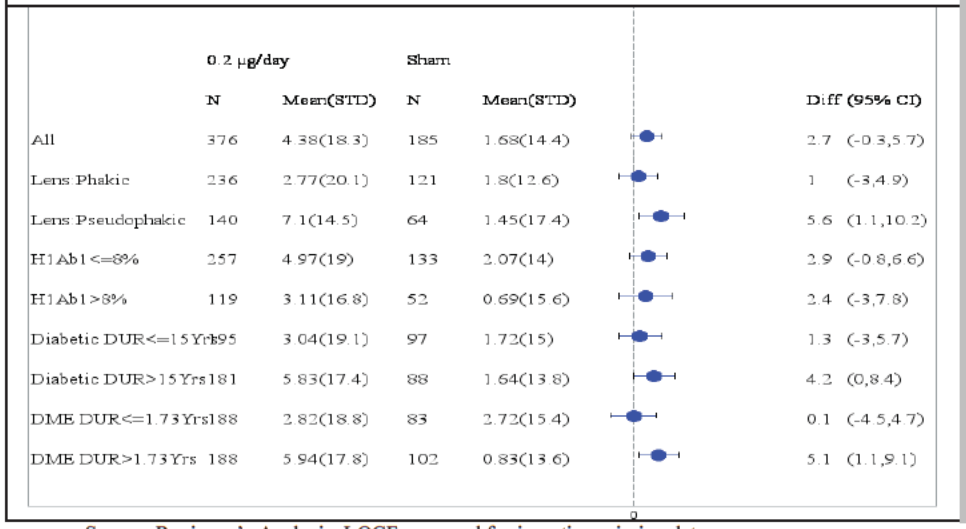
Figure 10: Subgroup Analysis: Mean BCVA Change from Baseline

Month 24

	0.2 µg/day		Sham		
	N	Mean(STD)	N	Mean(STD)	Diff(95% CI)
ALL	376	4.38(18.3)	185	1.68(14.4)	2.7 (-0.3,5.7)
Age <=65	214	5.95(18)	119	1.64(14.7)	4.3 (0.5,8.1)
Age >65	162	2.31(18.6)	66	1.76(13.9)	0.6 (-4.4,5.6)
Sex:Female	215	3.66(19)	108	1.51(15.9)	2.1 (-2,6.3)
Sex:Male	161	5.35(17.4)	77	1.92(12.1)	3.4 (-0.9,7.8)
Race:Asian	85	2.42(18.4)	40	2.95(11.2)	-0.5(-6.8,5.7)
Race:Black	22	12.09(14.7)	11	4.82(10)	7.3 (-2.8,17.3)
Race:Caucasian	265	4.37(18.6)	132	1.16(15.6)	3.2 (-0.5,6.9)
Race:Other	4	4.25(10.7)	2	-6.5(2.1)	10.8(-11.7,33.2)
Country:USA	246	6.5(17.9)	122	2.16(15.8)	4.3 (0.6,8.1)
Country:Other	130	0.37(18.6)	63	0.76(11.3)	-0.4(-5.4,4.6)

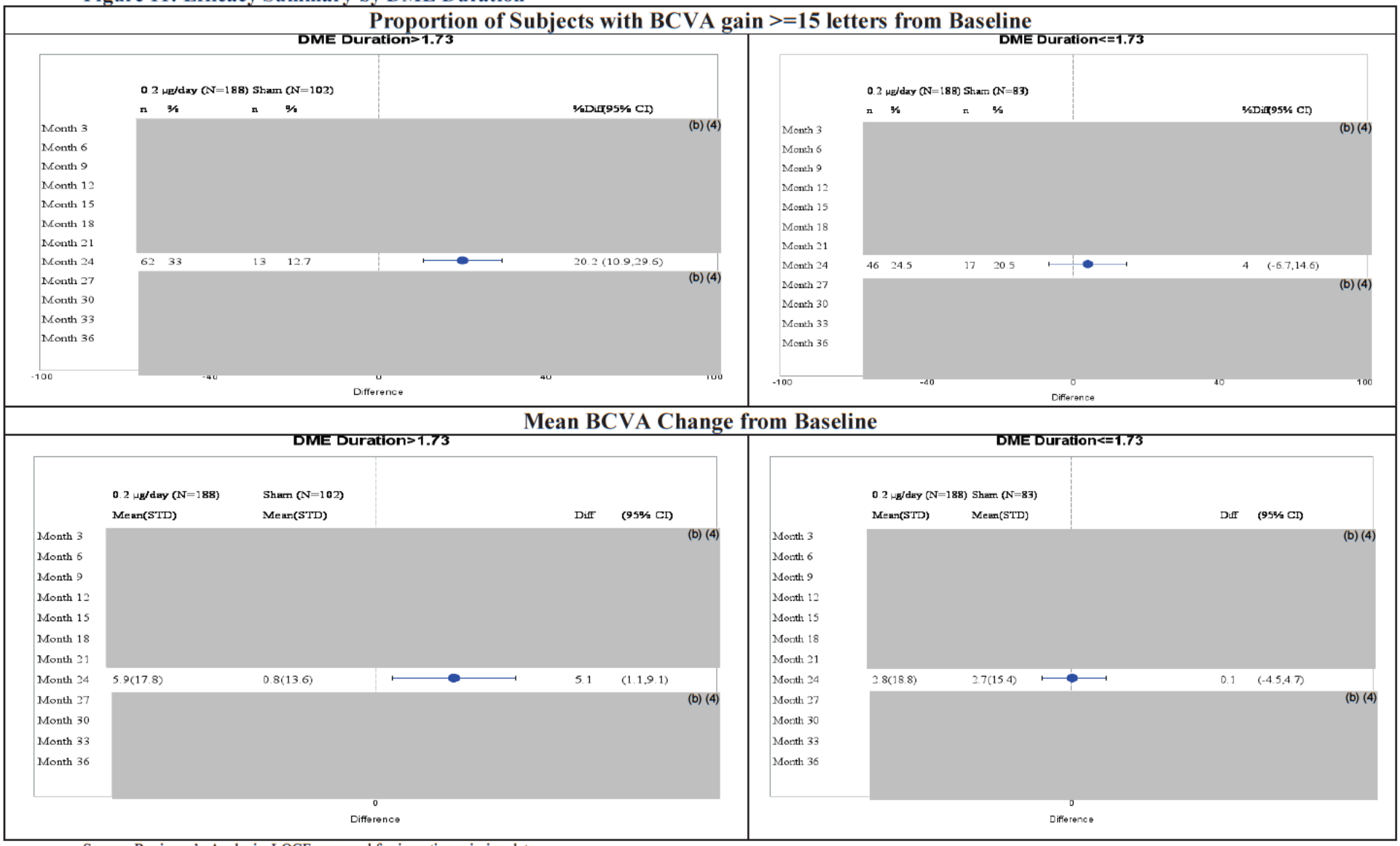


	0.2 µg/day		Sham		
	N	Mean(STD)	N	Mean(STD)	Diff (95% CI)
All	376	4.38(18.3)	185	1.68(14.4)	2.7 (-0.3,5.7)
Lens:Phakic	236	2.77(20.1)	121	1.8(12.6)	1 (-3,4.9)
Lens:Pseudophakic	140	7.1(14.5)	64	1.45(17.4)	5.6 (1.1,10.2)
H1Ab1<=8%	257	4.97(19)	133	2.07(14)	2.9 (-0.8,6.6)
H1Ab1>8%	119	3.11(16.8)	52	0.69(15.6)	2.4 (-3,7.8)
Diabetic DUR<=15Yrs	195	3.04(19.1)	97	1.72(15)	1.3 (-3,5.7)
Diabetic DUR>15Yrs	181	5.83(17.4)	88	1.64(13.8)	4.2 (0,8.4)
DME DUR<=1.73Yrs	188	2.82(18.8)	83	2.72(15.4)	0.1 (-4.5,4.7)
DME DUR>1.73Yrs	188	5.94(17.8)	102	0.83(13.6)	5.1 (1.1,9.1)



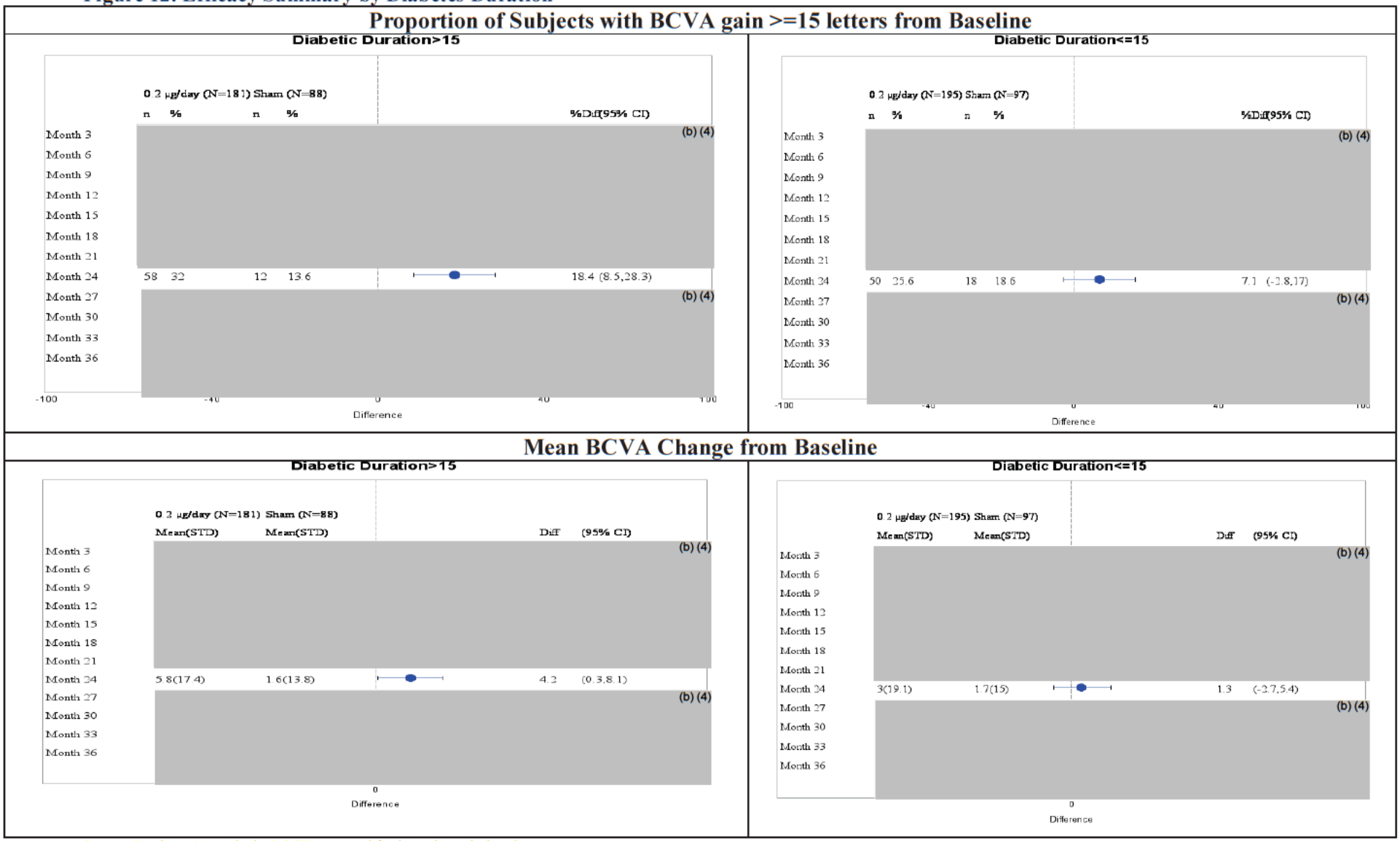
Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 11: Efficacy Summary by DME Duration



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Figure 12: Efficacy Summary by Diabetes Duration



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

5 Collective Evidence

There were more subjects in the ILUVIEN (0.2 µg/day) arm who gained at least 15 letters in BCVA from baseline at Month 24 compared to subjects in the Sham arm in both studies. However, there was no statistically significant difference between ILUVIEN (0.2 µg/day) and Sham in the proportion of subjects who gained at least 15 letters in BCVA from baseline at Month 36 in both studies. Additionally, there was no statistically significant difference between ILUVIEN (0.2 µg/day) and Sham in the mean change from baseline BCVA both at the Month 24 and Month 36 in Study A but the differences at both Month 24 and Month 36 were significant in Study B.

The two studies highlighted the safety issues associated with the study treatments. Two of the prominent adverse events associated with the study treatment were cataract formation and IOP related adverse events. The IOP-related adverse events included elevated IOP and ocular hypertension. A substantially large proportion of subjects in the two study treatments had IOP-related adverse events and required cataract surgery compared to the subjects randomized to the Sham arm. There were slightly more deaths in the ILUVIEN (0.2 µg/day) arm compared to the Sham arm. The risk-benefit analysis showed that the ILUVIEN (0.2 µg/day) arm had a less favorable safety profile when risk was measured by cataract surgery and elevated IOP.

6 Conclusion and recommendation

Based on the totality of the efficacy findings, this review concludes that there is evidence to support the efficacy of ILUVIEN (0.2 µg/day) for the treatment of DME provided the observed treatment effect is deemed clinically meaningful and outweigh the safety risks of cataract surgery and elevated IOP.

APPENDIX A: ADDITIONAL EFFICACY SUMMARIES

Table 10: Proportion of Subjects with a ≥ 15 letter Improvement in BCVA from Baseline by Visit (ITT LOCF)

Visit	0.5 µg/day N=196	0.2 µg/day N=190	Sham N=95	0.5 µg/day vs. Sham	0.2µg/day vs. Sham
Study A					
Month 3					(b) (4)
Month 6					
Month 9					
Month 12					
Month 15					
Month 18					
Month 21					
Month 24	(b) (4)	51(26.8%)	14(14.7%)	(b) (4)	12.1%(2.6%,21.6%)
Month 27					(b) (4)
Month 30					
Month 33					
Month 36					
Study B					
	0.5 µg/day N=199	0.2 µg/day N=186	Sham N=90	0.5 µg/day vs. Sham	0.2µg/day vs. Sham
Month 3					(b) (4)
Month 6					
Month 9					
Month 12					
Month 15					
Month 18					
Month 21					
Month 24	(b) (4)	57(30.6%)	16(17.8%)	(b) (4)	12.9%(2.6%,23.2%)
Month 27					(b) (4)
Month 30					
Month 33					
Month 36					

Source: Reviewer's Analysis. LOCF was used for imputing missing data

Table 11: Summary of the Mean Change from Baseline in BCVA by Visit (ITT LOCF)

Visit	0.5 µg/day N=196	0.2 µg/day N=190	Sham N=95	0.5 µg/day vs. Sham	0.2µg/day vs. Sham
Study A					
Baseline*	(b) (4)	53.4(13)	54.8(11.4)	(b) (4)	-1.4(-4.3,1.6)
Month 3					(b) (4)
Month 6					

Month 9					(b) (4)
Month 12					
Month 15					
Month 18					
Month 21					
Month 24	(b) (4)	3.7(18.8)	3.2(13.1)	(b) (4)	0.5(-3.3,4.3)
Month 27					(b) (4)
Month 30					
Month 33					
Month 36					
Study B					
	0.5 µg/day N=199	**0.2 µg/day N=186**	**Sham N=90**	**0.5 µg/day vs. Sham**	**0.2µg/day vs. Sham**
Baseline*	(b) (4)	53.3(12.4)	54.7(11.2)	(b) (4)	-1.4(-4.3,1.5)
Month 3					(b) (4)
Month 6					
Month 9					
Month 12					
Month 15					
Month 18					
Month 21					
Month 24	(b) (4)	5.1(18)	0(15.6)	(b) (4)	5.1(0.9,9.2)
Month 27					(b) (4)
Month 30					
Month 33					
Month 36					

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

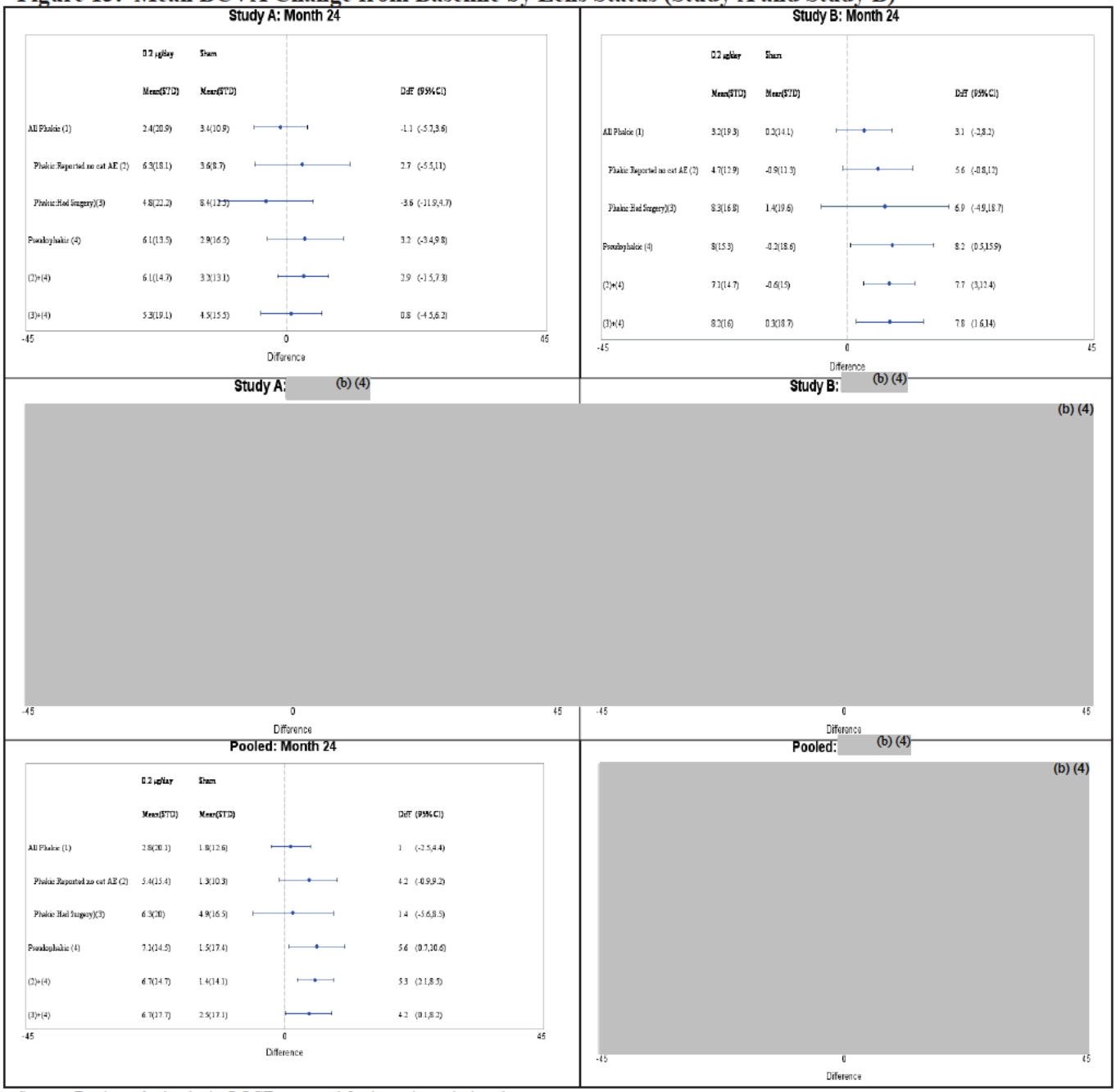
Table 12: Summary of Change from Baseline in Retinal Thickness at Center field (OCT) (ITT LOCF)

Visit	0.5 µg/day N=196	0.2 µg/day N=190	Sham N=95	0.5 µg/day vs. Sham	0.2µg/day vs. Sham
	Study A				
Month 3					(b) (4)
Month 6					
Month 9					
Month 12					
Month 15					
Month 18					
Month 21					
Month 24	(b) (4)	-165.3(196.3)	-97.2(201.2)	(b) (4)	-68(-118.2,-17.8)
Month 27					(b) (4)
Month 30					
Month 33					
Month 36					
	Study B				
	0.5 µg/day N=199	**0.2 µg/day N=186**	**Sham N=90**	**0.5 µg/day vs. Sham**	**0.2µg/day vs. Sham**
Month 3					(b) (4)
Month 6					
Month 9					
Month 12					
Month 15					
Month 18					
Month 21					
Month 24	(b) (4)	-171(188)	-126(231.7)	(b) (4)	-45(-100.5,10.6)
Month 27					(b) (4)
Month 30					
Month 36					

Source: Reviewer's Analysis. LOCF was used for imputing missing data.

APPENDIX B: ADDITIONAL SUMMARY FOR CONFOUNDING EFFECT OF CATARACT FORMATION AND SURGERY

Figure 13: Mean BCVA Change from Baseline by Lens Status (Study A and Study B)



Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Table 13: Proportion of subjects with ≥15 letters from Baseline at Month (b) (4) for subgroups based on lens status and cataract (ITT LOCF)

(b) (4)

Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Table 14: Proportion of subjects with ≥15 letters from Baseline at Month 24 for subgroups based on lens status and cataract (ITT LOCF)

Subgroup	0.5 µg/day	0.2 µg/day	Sham	0.5 µg/day vs. Sham	0.2µg/day vs. Sham
			Study A		
All Phakic (0)	(b) (4)	37/124(29.8%)	11/61(18%)	(b) (4)	11.8%(-0.8%,24.4%)
Pseudophakic (1)		14/66(21.2%)	3/34(8.8%)		12.4%(-1.3%,26.1%)
Phakic Subjects who had Cataract surgery (2)		37/95(38.9%)	5/14(35.7%)		3.2%(-23.7%,30.2%)
(1)+ (2)		51/161(31.7%)	8/48(16.7%)		15%(2.3%,27.8%)
Phakic subjects with No Cataract related AE (3)		6/23(26.1%)	5/34(14.7%)		11.4%(-10.2%,32.9%)
(1)+ (3)		20/89(22.5%)	8/68(11.8%)		10.7%(-0.9%,22.3%)
			Study B		
Phakic (0)	(b) (4)	32/112(28.6%)	11/60(18.3%)	(b) (4)	10.2%(-2.6%,23.1%)
Pseudophakic (1)		25/74(33.8%)	5/30(16.7%)		17.1%(0%,34.3%)
Phakic Subjects who had Cataract surgery (2)		28/74(37.8%)	4/14(28.6%)		9.3%(-16.9%,35.4%)
(1)+ (2)		53/148(35.8%)	9/44(20.5%)		15.4%(1.2%,29.6%)
Phakic subjects with No Cataract related AE (3)		4/26(15.4%)	4/35(11.4%)		4%(-13.5%,21.4%)
(1)+ (3)		29/100(29%)	9/65(13.8%)		15.2%(2.9%,27.4%)
			Pooled		
Phakic (0)	(b) (4)	69/236(29.2%)	22/121(18.2%)	(b) (4)	11.1%(2.1%,20.1%)
Pseudophakic (1)		39/140(27.9%)	8/64(12.5%)		15.4%(4.4%,26.3%)
Phakic Subjects who had Cataract surgery (2)		65/169(38.5%)	9/28(32.1%)		6.3%(-12.5%,25.1%)
(1)+ (2)		104/309(33.7%)	17/92(18.5%)		15.2%(5.7%,24.7%)
Phakic subjects with No Cataract related AE (3)		10/49(20.4%)	9/69(13%)		7.4%(-6.4%,21.2%)
(1)+ (3)		49/189(25.9%)	17/133(12.8%)		13.1%(4.7%,21.6%)

Source: Reviewer's Analysis. LOCF was used for imputing missing data.

Table 15: Mean Change from Baseline BCVA at Month (b) (4) for Subgroups based on Lens and Cataract Status (ITT LOCF)

(b) (4)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

Table 16: Mean Change from Baseline BCVA at Month 24 for Subgroups based on Lens and Cataract Status (ITT LOCF)

Subgroup	0.5 µg/day	0.2 µg/day	Sham	0.5 µg/day vs. Sham	0.2µg/day vs. Sham
	Study A				
Phakic (0)	(b) (4)	2.4(20.9)	3.4(10.9)	(b) (4)	-1.1(-5.7,3.6)
Pseudophakic (1)		6.1(13.5)	2.9(16.5)		3.2(-3.4,9.8)
Phakic Subjects who had Cataract surgery (2)		4.8(22.2)	8.4(12.5)		-3.6(-11.9,4.7)
(1)+ (2)		5.3(19.1)	4.5(15.5)		0.8(-4.5,6.2)

Phakic subjects with No Cataract related AE (3)	(b) (4)	6.3(18.1)	3.6(8.7)	(b) (4) 2.7(-5.5,11)
(1)+ (3)		6.1(14.7)	3.2(13.1)	2.9(-1.5,7.3)
		Study B		
Phakic (0)		3.2(19.3)	0.2(14.1)	3.1(-2,8.2)
Pseudophakic (1)		8(15.3)	-0.2(18.6)	8.2(0.5,15.9)
Phakic Subjects who had Cataract surgery (2)		8.3(16.8)	1.4(19.6)	6.9(-4.9,18.7)
(1)+ (2)		8.2(16)	0.3(18.7)	7.8(1.6,14)
Phakic subjects with No Cataract related AE (3)		4.7(12.9)	-0.9(11.3)	5.6(-0.8,12)
(1)+ (3)		7.1(14.7)	-0.6(15)	7.7(3,12.4)
		Pooled		
Phakic (0)	(b) (4)	2.8(20.1)	1.8(12.6)	(b) (4) 1(-2.5,4.4)
Pseudophakic (1)		7.1(14.5)	1.5(17.4)	5.6(0.7,10.6)
Phakic Subjects who had Cataract surgery (2)		6.3(20)	4.9(16.5)	1.4(-5.6,8.5)
(1)+ (2)		6.7(17.7)	2.5(17.1)	4.2(0.1,8.2)
Phakic subjects with No Cataract related AE (3)		5.4(15.4)	1.3(10.3)	4.2(-0.9,9.2)
(1)+ (3)		6.7(14.7)	1.4(14.1)	5.3(2.1,8.5)

Source: Reviewer's Analysis. LOCF was used for imputing missing data. Confidence interval for difference in means was computed using the normal approximation with unequal variance assumed for each arm using the SAS t-test procedure without adjusting for baseline measurements.

APPENDIX C: ADDITIONAL SAFETY SUMMARIES

Table 17: Summary of Adverse Events within 24 Months (AE) (Pooled: All Treated Subjects)

	Treatment: N (%)			% Difference (95% CI)	
Adverse Events (AE)	0.5 µg/day N=393	0.2 µg/day N=375	Sham N=185	0.5 µg/day vs. Sham	0.2 µg/day vs. Sham
Any AE	388(98.7%)	365(97.3%)	171(92.4%)	6.3%(2.3%,10.3%)	4.9%(0.8%,9%)
Any Ocular AE	369(93.9%)	324(86.4%)	131(70.8%)	23.1%(16.1%,30%)	15.6%(8.2%,23%)
Any Serious AE	317(80.7%)	266(70.9%)	91(49.2%)	31.5%(23.3%,39.7%)	21.7%(13.2%,30.3%)
Any Ocular Serious AE	247(62.8%)	186(49.6%)	42(22.7%)	40.1%(32.4%,47.8%)	26.9%(19%,34.8%)
Any Severe AE	228(58%)	193(51.5%)	73(39.5%)	18.6%(10%,27.1%)	12%(3.3%,20.7%)
Any Ocular Severe AE	135(34.4%)	106(28.3%)	27(14.6%)	19.8%(12.8%,26.7%)	13.7%(6.8%,20.5%)
Any IOP Related AE	169(43%)	123(32.8%)	19(10.3%)	32.7%(26.2%,39.3%)	22.5%(16.1%,29%)
≥10 mm Hg IOP Change from Baseline at any visit	158(40.2%)	110(29.3%)	12(6.5%)	33.7%(27.7%,39.7%)	22.8%(17%,28.7%)
≥25 mm Hg IOP at any visit	163(41.5%)	112(29.9%)	18(9.7%)	31.7%(25.3%,38.2%)	20.1%(13.8%,26.4%)
≥30 mm Hg IOP at any visit	89(22.6%)	67(17.9%)	5(2.7%)	19.9%(15.2%,24.7%)	15.2%(10.6%,19.7%)
Glaucoma	12(3.1%)	12(3.2%)	4(2.2%)	0.9%(-1.8%,3.6%)	1%(-1.7%,3.8%)
IOP Lowering surgery	32(8.1%)	18(4.8%)	1(0.5%)	7.6%(4.7%,10.5%)	4.3%(1.9%,6.7%)
Any IOP Lowering Procedures	186(47.3%)	144(38.4%)	26(14.1%)	33.3%(26.2%,40.3%)	24.3%(17.3%,31.4%)
Trabeluctomy	22(5.6%)	10(2.7%)	0(0%)	5.6%(3.3%,7.9%)	2.7%(1%,4.3%)
Any Cataract Related AE Baseline Phakic Subjects	235(88.7%)	187(79.6%)	52(43%)	45.7%(36.1%,55.3%)	36.6%(26.4%,46.8%)
Cataract Surgery in Baseline Phakic Subjects	220(83%)	169(71.9%)	28(23.1%)	59.9%(51.1%,68.6%)	48.8%(39.3%,58.2%)
Death	21(5.3%)	23(6.1%)	5(2.7%)	2.6%(-0.6%,5.9%)	3.4%(0.1%,6.8%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

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Table 18: Summary of Adverse Events within 24 Months (AE) (Study A)

	Treatment: N (%)			% Difference (95% CI)	
Adverse Events (AE)	0.5 µg/day N=195	0.2 µg/day N=190	Sham N=95	0.5 µg/day vs. Sham	0.2 µg/day vs. Sham
Any AE	192(98.5%)	185(97.4%)	90(94.7%)	3.7%(-1.1%,8.5%)	2.6%(-2.4%,7.7%)
Any Ocular AE	187(95.9%)	168(88.4%)	71(74.7%)	21.2%(12%,30.3%)	13.7%(3.8%,23.5%)
Any Serious AE	155(79.5%)	140(73.7%)	51(53.7%)	25.8%(14.3%,37.3%)	20%(8.2%,31.8%)
Any Ocular Serious AE	121(62.1%)	105(55.3%)	22(23.2%)	38.9%(28%,49.8%)	32.1%(21.1%,43.1%)
Any Severe AE	106(54.4%)	104(54.7%)	34(35.8%)	18.6%(6.7%,30.5%)	18.9%(7%,30.9%)
Any Ocular Severe AE	65(33.3%)	61(32.1%)	14(14.7%)	18.6%(8.9%,28.3%)	17.4%(7.6%,27.1%)
Any IOP Related AE	93(47.7%)	73(38.4%)	8(8.4%)	39.3%(30.3%,48.2%)	30%(21.1%,38.9%)
≥10 mm Hg IOP Change from Baseline at any visit	87(44.6%)	62(32.6%)	5(5.3%)	39.4%(31.1%,47.6%)	27.4%(19.3%,35.4%)
≥25 mm Hg IOP at any visit	90(46.2%)	61(32.1%)	9(9.5%)	36.7%(27.5%,45.8%)	22.6%(13.8%,31.5%)
≥30 mm Hg IOP at any visit	49(25.1%)	35(18.4%)	2(2.1%)	23%(16.3%,29.8%)	16.3%(10.1%,22.5%)
Glaucoma	5(2.6%)	6(3.2%)	3(3.2%)	-0.6%(-4.8%,3.6%)	0%(-4.3%,4.3%)
IOP Lowering surgery	14(7.2%)	9(4.7%)	0(0%)	7.2%(3.6%,10.8%)	4.7%(1.7%,7.8%)
Any IOP Lowering	96(49.2%)	79(41.6%)	13(13.7%)	35.5%(25.7%,45.4%)	27.9%(18.1%,37.7%)

Procedures					
Trabeluctomy	10(5.1%)	5(2.6%)	0(0%)	5.1%(2%,8.2%)	2.6%(0.4%,4.9%)
Any Cataract Related AE Baseline Phakic Subjects	115(88.5%)	101(81.5%)	27(44.3%)	44.2%(30.6%,57.8%)	37.2%(23%,51.4%)
Cataract Surgery in Baseline Phakic Subjects	106(81.5%)	95(76.6%)	14(23%)	58.6%(46.1%,71.1%)	53.7%(40.7%,66.6%)
Death	13(6.7%)	9(4.7%)	4(4.2%)	2.5%(-2.9%,7.8%)	0.5%(-4.5%,5.6%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 19: Summary of Adverse Events within 24 Months (AE) (Study B)

	Treatment: N (%)			**% Difference (95% CI)**	
Adverse Events (AE)	**0.5 µg/day N=198**	**0.2 µg/day N=185**	**Sham N=90**	**0.5 µg/day vs. Sham**	**0.2 µg/day vs. Sham**
Any AE	196(99%)	180(97.3%)	81(90%)	9%(2.6%,15.3%)	7.3%(0.7%,13.9%)
Any Ocular AE	182(91.9%)	156(84.3%)	60(66.7%)	25.3%(14.8%,35.7%)	17.7%(6.6%,28.7%)
Any Serious AE	162(81.8%)	126(68.1%)	40(44.4%)	37.4%(25.8%,49%)	23.7%(11.4%,35.9%)
Any Ocular Serious AE	126(63.6%)	81(43.8%)	20(22.2%)	41.4%(30.5%,52.3%)	21.6%(10.4%,32.7%)
Any Severe AE	122(61.6%)	89(48.1%)	39(43.3%)	18.3%(6%,30.6%)	4.8%(-7.7%,17.3%)
Any Ocular Severe AE	70(35.4%)	45(24.3%)	13(14.4%)	20.9%(11.1%,30.8%)	9.9%(0.3%,19.4%)
Any IOP Related AE	76(38.4%)	50(27%)	11(12.2%)	26.2%(16.6%,35.7%)	14.8%(5.5%,24.1%)
≥10 mm Hg IOP Change from Baseline at any visit	71(35.9%)	48(25.9%)	7(7.8%)	28.1%(19.4%,36.8%)	18.2%(9.8%,26.6%)
≥25 mm Hg IOP at any visit	73(36.9%)	51(27.6%)	9(10%)	26.9%(17.7%,36%)	17.6%(8.6%,26.5%)
≥30 mm Hg IOP at any visit	40(20.2%)	32(17.3%)	3(3.3%)	16.9%(10.2%,23.6%)	14%(7.4%,20.6%)
Glaucoma	7(3.5%)	6(3.2%)	1(1.1%)	2.4%(-0.9%,5.8%)	2.1%(-1.2%,5.5%)
IOP Lowering surgery	18(9.1%)	9(4.9%)	1(1.1%)	8%(3.4%,12.5%)	3.8%(0%,7.5%)
Any IOP Lowering Procedures	90(45.5%)	65(35.1%)	13(14.4%)	31%(21%,41.1%)	20.7%(10.7%,30.7%)
Trabeluctomy	12(6.1%)	5(2.7%)	0(0%)	6.1%(2.7%,9.4%)	2.7%(0.4%,5%)
Any Cataract Related AE Baseline Phakic Subjects	120(88.9%)	86(77.5%)	25(41.7%)	47.2%(33.7%,60.8%)	35.8%(21.1%,50.5%)
Cataract Surgery in Baseline Phakic Subjects	114(84.4%)	74(66.7%)	14(23.3%)	61.1%(48.8%,73.4%)	43.3%(29.5%,57.2%)
Death	8(4%)	14(7.6%)	1(1.1%)	2.9%(-0.6%,6.4%)	6.5%(2.1%,10.8%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

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Table 20: Summary of Adverse Events within three years (AE) (Study A)

	Treatment: N (%)			**% Difference (95% CI)**	
Adverse Events (AE)	**0.5 µg/day N=195**	**0.2 µg/day N=190**	**Sham N=95**	**0.5 µg/day vs. Sham**	**0.2 µg/day vs. Sham**
Any AE	192(98.5%)	186(97.9%)	92(96.8%)	1.6%(-2.3%,5.5%)	1.1%(-3%,5.1%)
Any Ocular AE	187(95.9%)	171(90%)	74(77.9%)	18%(9.2%,26.8%)	12.1%(2.7%,21.5%)
Any Serious AE	163(83.6%)	149(78.4%)	64(67.4%)	16.2%(5.5%,27%)	11.1%(0%,22.1%)
Any Ocular Serious AE	130(66.7%)	114(60%)	25(26.3%)	40.4%(29.3%,51.4%)	33.7%(22.4%,45%)
Any Severe AE	117(60%)	115(60.5%)	42(44.2%)	15.8%(3.7%,27.9%)	16.3%(4.1%,28.5%)
Any Ocular Severe AE	69(35.4%)	65(34.2%)	16(16.8%)	18.5%(8.5%,28.6%)	17.4%(7.3%,27.5%)

Any IOP Related AE	96(49.2%)	80(42.1%)	9(9.5%)	39.8%(30.6%,48.9%)	32.6%(23.5%,41.8%)
≥10 mm Hg IOP Change from Baseline at any visit	90(46.2%)	72(37.9%)	8(8.4%)	37.7%(28.8%,46.7%)	29.5%(20.6%,38.3%)
≥25 mm Hg IOP at any visit	93(47.7%)	73(38.4%)	11(11.6%)	36.1%(26.6%,45.6%)	26.8%(17.4%,36.3%)
≥30 mm Hg IOP at any visit	53(27.2%)	40(21.1%)	4(4.2%)	23%(15.5%,30.4%)	16.8%(9.8%,23.9%)
Glaucoma	6(3.1%)	8(4.2%)	3(3.2%)	-0.1%(-4.4%,4.2%)	1.1%(-3.5%,5.6%)
IOP Lowering surgery	14(7.2%)	9(4.7%)	0(0%)	7.2%(3.6%,10.8%)	4.7%(1.7%,7.8%)
Any IOP Lowering Procedures	96(49.2%)	79(41.6%)	13(13.7%)	35.5%(25.7%,45.4%)	27.9%(18.1%,37.7%)
Trabeluctomy	10(5.1%)	5(2.6%)	0(0%)	5.1%(2%,8.2%)	2.6%(0.4%,4.9%)
Any Cataract Related AE Baseline Phakic Subjects	115(88.5%)	102(82.3%)	33(54.1%)	34.4%(20.7%,48%)	28.2%(14%,42.4%)
Cataract Surgery in Baseline Phakic Subjects	111(85.4%)	103(83.1%)	15(24.6%)	60.8%(48.4%,73.2%)	58.5%(45.8%,71.1%)
Death	19(9.7%)	12(6.3%)	6(6.3%)	3.4%(-3%,9.9%)	0%(-6%,6%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 21: Summary of Adverse Events within three years (AE) (Study B)

	Treatment: N (%)			**% Difference (95% CI)**	
Adverse Events (AE)	**0.5 µg/day N=198**	**0.2 µg/day N=185**	**Sham N=90**	**0.5 µg/day vs. Sham**	**0.2 µg/day vs. Sham**
Any AE	197(99.5%)	183(98.9%)	83(92.2%)	7.3%(1.7%,12.9%)	6.7%(1%,12.4%)
Any Ocular AE	186(93.9%)	165(89.2%)	63(70%)	23.9%(13.9%,34%)	19.2%(8.7%,29.7%)
Any Serious AE	168(84.8%)	143(77.3%)	48(53.3%)	31.5%(20.1%,43%)	24%(12%,35.9%)
Any Ocular Serious AE	135(68.2%)	99(53.5%)	24(26.7%)	41.5%(30.3%,52.7%)	26.8%(15.2%,38.5%)
Any Severe AE	132(66.7%)	102(55.1%)	43(47.8%)	18.9%(6.7%,31.1%)	7.4%(-5.2%,19.9%)
Any Ocular Severe AE	75(37.9%)	55(29.7%)	15(16.7%)	21.2%(11%,31.5%)	13.1%(2.9%,23.2%)
Any IOP Related AE	83(41.9%)	59(31.9%)	13(14.4%)	27.5%(17.5%,37.5%)	17.4%(7.6%,27.3%)
≥10 mm Hg IOP Change from Baseline at any visit	81(40.9%)	55(29.7%)	10(11.1%)	29.8%(20.4%,39.2%)	18.6%(9.4%,27.9%)
≥25 mm Hg IOP at any visit	83(41.9%)	60(32.4%)	12(13.3%)	28.6%(18.8%,38.4%)	19.1%(9.4%,28.8%)
≥30 mm Hg IOP at any visit	47(23.7%)	35(18.9%)	4(4.4%)	19.3%(12%,26.6%)	14.5%(7.4%,21.5%)
Glaucoma	12(6.1%)	11(5.9%)	1(1.1%)	4.9%(1%,8.9%)	4.8%(0.8%,8.9%)
IOP Lowering surgery	18(9.1%)	9(4.9%)	1(1.1%)	8%(3.4%,12.5%)	3.8%(0%,7.5%)
Any IOP Lowering Procedures	90(45.5%)	65(35.1%)	13(14.4%)	31%(21%,41.1%)	20.7%(10.7%,30.7%)
Trabeluctomy	12(6.1%)	5(2.7%)	0(0%)	6.1%(2.7%,9.4%)	2.7%(0.4%,5%)
Any Cataract Related AE Baseline Phakic Subjects	120(88.9%)	90(81.1%)	28(46.7%)	42.2%(28.5%,55.9%)	34.4%(19.8%,49%)
Cataract Surgery in Baseline Phakic Subjects	120(88.9%)	85(76.6%)	18(30%)	58.9%(46.1%,71.6%)	46.6%(32.6%,60.6%)
Death	12(6.1%)	16(8.6%)	5(5.6%)	0.5%(-5.3%,6.3%)	3.1%(-3.1%,9.3%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 22: Summary of Adverse Events within three years (AE) (Pooled: Psuedophakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	0.5 µg/day N=128	0.2 µg/day N=140	Sham N=64	0.5 µg/day vs. Sham	0.2 µg/day vs. Sham
Any AE	128(100%)	138(98.6%)	61(95.3%)	4.7%(-0.5%,9.9%)	3.3%(-2.3%,8.8%)
Any Ocular AE	116(90.6%)	117(83.6%)	43(67.2%)	23.4%(10.9%,36%)	16.4%(3.3%,29.4%)
Any Serious AE	83(64.8%)	80(57.1%)	34(53.1%)	11.7%(-3%,26.5%)	4%(-10.7%,18.7%)
Any Ocular Serious AE	30(23.4%)	22(15.7%)	8(12.5%)	10.9%(0%,21.9%)	3.2%(-6.9%,13.3%)
Any Severe AE	72(56.3%)	64(45.7%)	28(43.8%)	12.5%(-2.4%,27.4%)	2%(-12.7%,16.7%)
Any Ocular Severe AE	19(14.8%)	17(12.1%)	10(15.6%)	-0.8%(-11.6%,10%)	-3.5%(-13.9%,6.9%)
Any IOP Related AE	66(51.6%)	58(41.4%)	10(15.6%)	35.9%(23.5%,48.4%)	25.8%(13.7%,37.9%)
≥10 mm Hg IOP Change from Baseline at any visit	65(50.8%)	52(37.1%)	8(12.5%)	38.3%(26.4%,50.1%)	24.6%(13.3%,36%)
≥25 mm Hg IOP at any visit	65(50.8%)	53(37.9%)	12(18.8%)	32%(19.1%,44.9%)	19.1%(6.6%,31.6%)
≥35 mm Hg IOP at any visit	38(29.7%)	29(20.7%)	5(7.8%)	21.9%(11.6%,32.2%)	12.9%(3.5%,22.3%)
Glaucoma	9(7%)	8(5.7%)	2(3.1%)	3.9%(-2.2%,10.1%)	2.6%(-3.2%,8.3%)
IOP Lowering surgery	14(10.9%)	6(4.3%)	1(1.6%)	9.4%(3.2%,15.6%)	2.7%(-1.8%,7.2%)
Any IOP Lowering Procedures	68(53.1%)	56(40%)	12(18.8%)	34.4%(21.5%,47.3%)	21.3%(8.7%,33.8%)
Trabelcotomy	9(7%)	3(2.1%)	0(0%)	7%(2.6%,11.5%)	2.1%(-0.3%,4.5%)
Death	12(9.4%)	10(7.1%)	1(1.6%)	7.8%(1.9%,13.7%)	5.6%(0.3%,10.8%)

Table 23: Summary of Adverse Events within three years (AE) (Pooled: Phakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	0.5 µg/day N=265	0.2 µg/day N=235	Sham N=121	0.5 µg/day vs. Sham	0.2 µg/day vs. Sham
Any AE	261(98.5%)	231(98.3%)	114(94.2%)	4.3%(-0.1%,8.7%)	4.1%(-0.4%,8.6%)
Any Ocular AE	257(97%)	219(93.2%)	94(77.7%)	19.3%(11.6%,27%)	15.5%(7.4%,23.6%)
Any Serious AE	248(93.6%)	212(90.2%)	78(64.5%)	29.1%(20.1%,38.1%)	25.7%(16.4%,35.1%)
Any Ocular Serious AE	235(88.7%)	191(81.3%)	41(33.9%)	54.8%(45.5%,64.1%)	47.4%(37.6%,57.2%)
Any Severe AE	177(66.8%)	153(65.1%)	57(47.1%)	19.7%(9.1%,30.2%)	18%(7.2%,28.8%)
Any Ocular Severe AE	125(47.2%)	103(43.8%)	21(17.4%)	29.8%(20.8%,38.9%)	26.5%(17.2%,35.7%)
Any IOP Related AE	113(42.6%)	81(34.5%)	12(9.9%)	32.7%(24.7%,40.7%)	24.6%(16.5%,32.6%)
≥10 mm Hg IOP Change from Baseline at any visit	106(40%)	75(31.9%)	10(8.3%)	31.7%(24.1%,39.4%)	23.7%(15.9%,31.4%)
≥25 mm Hg IOP at any visit	111(41.9%)	80(34%)	11(9.1%)	32.8%(25%,40.6%)	25%(17%,32.9%)
≥35 mm Hg IOP at any visit	62(23.4%)	46(19.6%)	3(2.5%)	20.9%(15.1%,26.7%)	17.1%(11.3%,22.9%)
Glaucoma	9(3.4%)	11(4.7%)	2(1.7%)	1.7%(-1.4%,4.9%)	3%(-0.5%,6.6%)
IOP Lowering surgery	18(6.8%)	12(5.1%)	0(0%)	6.8%(3.8%,9.8%)	5.1%(2.3%,7.9%)
Any IOP Lowering Procedures	118(44.5%)	88(37.4%)	14(11.6%)	33%(24.7%,41.2%)	25.9%(17.5%,34.3%)
Trabelcotomy	13(4.9%)	7(3%)	0(0%)	4.9%(2.3%,7.5%)	3%(0.8%,5.2%)
Any Cataract Related AE	235(88.7%)	192(81.7%)	61(50.4%)	38.3%(28.6%,48%)	31.3%(21.1%,41.5%)
Cataract Surgery	231(87.2%)	188(80%)	33(27.3%)	59.9%(51%,68.8%)	52.7%(43.3%,62.2%)
Death	19(7.2%)	18(7.7%)	10(8.3%)	-1.1%(-6.9%,4.7%)	-0.6%(-6.6%,5.4%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (Absolute glaucoma, Ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 24: Summary of Adverse Events within 24 Month (AE) (Pooled: Psuedophakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	0.5 µg/day N=128	0.2 µg/day N=140	Sham N=64	0.5 µg/day vs. Sham	0.2 µg/day vs. Sham
Any AE	127(99.2%)	137(97.9%)	60(93.8%)	5.5%(-0.7%,11.6%)	4.1%(-2.3%,10.5%)
Any Ocular AE	112(87.5%)	111(79.3%)	39(60.9%)	26.6%(13.3%,39.8%)	18.3%(4.6%,32.1%)
Any Serious AE	76(59.4%)	67(47.9%)	23(35.9%)	23.4%(8.9%,37.9%)	11.9%(-2.5%,26.3%)
Any Ocular Serious AE	23(18%)	13(9.3%)	8(12.5%)	5.5%(-5%,16%)	-3.2%(-12.6%,6.2%)
Any Severe AE	64(50%)	53(37.9%)	24(37.5%)	12.5%(-2.2%,27.2%)	0.4%(-14%,14.7%)
Any Ocular Severe AE	15(11.7%)	12(8.6%)	10(15.6%)	-3.9%(-14.4%,6.6%)	-7.1%(-17.1%,3%)
Any IOP Related AE	65(50.8%)	50(35.7%)	8(12.5%)	38.3%(26.4%,50.1%)	23.2%(11.9%,34.6%)
≥10 mm Hg IOP Change from Baseline at any visit	64(50%)	47(33.6%)	4(6.3%)	43.8%(33.3%,54.2%)	27.3%(17.5%,37.1%)
≥25 mm Hg IOP at any visit	62(48.4%)	45(32.1%)	9(14.1%)	34.4%(22.2%,46.5%)	18.1%(6.6%,29.6%)
≥35 mm Hg IOP at any visit	35(27.3%)	27(19.3%)	3(4.7%)	22.7%(13.4%,32%)	14.6%(6.3%,22.9%)
Glaucoma	7(5.5%)	3(2.1%)	2(3.1%)	2.3%(-3.5%,8.1%)	-1%(-5.9%,3.9%)
IOP Lowering surgery	14(10.9%)	6(4.3%)	1(1.6%)	9.4%(3.2%,15.6%)	2.7%(-1.8%,7.2%)
Any IOP Lowering Procedures	68(53.1%)	56(40%)	12(18.8%)	34.4%(21.5%,47.3%)	21.3%(8.7%,33.8%)
Trabelcotomy	9(7%)	3(2.1%)	0(0%)	7%(2.6%,11.5%)	2.1%(-0.3%,4.5%)
Death	8(6.3%)	7(5%)	1(1.6%)	4.7%(-0.5%,9.9%)	3.4%(-1.3%,8.2%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

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Table 25: Summary of Adverse Events within 24 Months (AE) (Pooled: Phakic Subjects)

Adverse Events (AE)	Treatment: N (%)			% Difference (95% CI)	
	0.5 µg/day N=265	0.2 µg/day N=235	Sham N=121	0.5 µg/day vs. Sham	0.2 µg/day vs. Sham
Any AE	261(98.5%)	228(97%)	111(91.7%)	6.8%(1.6%,11.9%)	5.3%(-0.1%,10.7%)
Any Ocular AE	257(97%)	213(90.6%)	92(76%)	20.9%(13.1%,28.8%)	14.6%(6.1%,23.1%)
Any Serious AE	241(90.9%)	199(84.7%)	68(56.2%)	34.7%(25.3%,44.2%)	28.5%(18.5%,38.5%)
Any Ocular Serious AE	224(84.5%)	173(73.6%)	34(28.1%)	56.4%(47.3%,65.5%)	45.5%(35.7%,55.3%)
Any Severe AE	164(61.9%)	140(59.6%)	49(40.5%)	21.4%(10.9%,31.9%)	19.1%(8.3%,29.8%)
Any Ocular Severe AE	120(45.3%)	94(40%)	17(14%)	31.2%(22.6%,39.9%)	26%(17.1%,34.8%)
Any IOP Related AE	104(39.2%)	73(31.1%)	11(9.1%)	30.2%(22.4%,38%)	22%(14.1%,29.8%)
≥10 mm Hg IOP Change from Baseline at any visit	94(35.5%)	63(26.8%)	8(6.6%)	28.9%(21.6%,36.1%)	20.2%(13%,27.4%)
≥25 mm Hg IOP at any visit	101(38.1%)	67(28.5%)	9(7.4%)	30.7%(23.2%,38.2%)	21.1%(13.6%,28.5%)
≥30 mm Hg IOP at any visit	54(20.4%)	40(17%)	2(1.7%)	18.7%(13.4%,24.1%)	15.4%(10.1%,20.7%)
Glaucoma	5(1.9%)	9(3.8%)	2(1.7%)	0.2%(-2.6%,3%)	2.2%(-1.2%,5.5%)
IOP Lowering surgery	18(6.8%)	12(5.1%)	0(0%)	6.8%(3.8%,9.8%)	5.1%(2.3%,7.9%)
Any IOP Lowering Procedures	118(44.5%)	88(37.4%)	14(11.6%)	33%(24.7%,41.2%)	25.9%(17.5%,34.3%)
Trabeluctomy	13(4.9%)	7(3%)	0(0%)	4.9%(2.3%,7.5%)	3%(0.8%,5.2%)
Any Cataract Related AE Baseline Phakic Subjects	235(88.7%)	187(79.6%)	52(43%)	45.7%(36.1%,55.3%)	36.6%(26.4%,46.8%)

Cataract Surgery in Baseline Phakic Subjects	220(83%)	169(71.9%)	28(23.1%)	59.9%(51.1%,68.6%)	48.8%(39.3%,58.2%)
Death	13(4.9%)	16(6.8%)	4(3.3%)	1.6%(-2.5%,5.7%)	3.5%(-1%,8%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 26: Summary of Adverse Events (AE) (Subjects who lost 15 letters or more at Month 24

	Treatment: N (%)			% Difference (95% CI)	
Adverse Events (AE)	**0.5 µg/day N=42**	**0.2 µg/day N=48**	**Sham N=14**	**0.5 µg/day vs. Sham**	**0.2 µg/day vs. Sham**
Any AE	42(100%)	47(97.9%)	14(100%)	-2.1%(-6.1%,2%)	-2.1%(-6.1%,2%)
Any Ocular AE	41(97.6%)	44(91.7%)	13(92.9%)	4.8%(-9.5%,19%)	-1.2%(-16.8%,14.4%)
Any Serious AE	33(78.6%)	34(70.8%)	12(85.7%)	-7.1%(-29.3%,15%)	-14.9%(-37.3%,7.5%)
Any Ocular Serious AE	24(57.1%)	23(47.9%)	8(57.1%)	0%(-29.9%,29.9%)	-9.2%(-38.8%,20.3%)
Any Severe AE	29(69%)	32(66.7%)	9(64.3%)	4.8%(-24%,33.5%)	2.4%(-26%,30.8%)
Any Ocular Severe AE	19(45.2%)	20(41.7%)	6(42.9%)	2.4%(-27.6%,32.4%)	-1.2%(-30.6%,28.2%)
Any IOP Related AE	24(57.1%)	21(43.8%)	5(35.7%)	21.4%(-7.8%,50.7%)	8%(-20.7%,36.8%)
≥10 mm Hg IOP Change from Baseline at any visit	23(54.8%)	17(35.4%)	3(21.4%)	33.3%(7.1%,59.6%)	14%(-11.4%,39.4%)
≥25 mm Hg IOP at any visit	23(54.8%)	21(43.8%)	4(28.6%)	26.2%(-1.9%,54.2%)	15.2%(-12.3%,42.7%)
≥30 mm Hg IOP at any visit	17(40.5%)	12(25%)	3(21.4%)	19%(-7.1%,45.2%)	3.6%(-21.2%,28.3%)
Glaucoma	5(11.9%)	4(8.3%)	2(14.3%)	-2.4%(-23.2%,18.4%)	-6%(-25.9%,14%)
IOP Lowering surgery	7(16.7%)	2(4.2%)	1(7.1%)	9.5%(-8.1%,27.1%)	-3%(-17.6%,11.7%)
Any IOP Lowering Procedures	24(57.1%)	23(47.9%)	7(50%)	7.1%(-23%,37.3%)	-2.1%(-31.8%,27.7%)
Trabeluctomy	3(7.1%)	1(2.1%)	0(0%)	7.1%(-0.6%,14.9%)	2.1%(-2%,6.1%)
Any Cataract Related AE Baseline Phakic Subjects	26(89.7%)	36(87.8%)	5(71.4%)	18.2%(-17%,53.5%)	16.4%(-18.6%,51.3%)
Cataract Surgery in Baseline Phakic Subjects	17(58.6%)	21(51.2%)	2(28.6%)	30%(-7.9%,68%)	22.6%(-14.1%,59.4%)
Death	2(4.8%)	3(6.3%)	0(0%)	4.8%(-1.7%,11.2%)	6.3%(-0.6%,13.1%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 27: Summary of Adverse Events (AE) (Subjects who lost 15 letters or more at Month 36

	Treatment: N (%)			% Difference (95% CI)	
Adverse Events (AE)	**0.5 µg/day N=38**	**0.2 µg/day N=42**	**Sham N=20**	**0.5 µg/day vs. Sham**	**0.2 µg/day vs. Sham**
Any AE	38(100%)	41(97.6%)	18(90%)	10%(-3.1%,23.1%)	7.6%(-6.3%,21.6%)
Any Ocular AE	37(97.4%)	38(90.5%)	16(80%)	17.4%(-0.9%,35.6%)	10.5%(-9.2%,30.1%)
Any Serious AE	32(84.2%)	33(78.6%)	15(75%)	9.2%(-13%,31.4%)	3.6%(-19.1%,26.2%)
Any Ocular Serious AE	27(71.1%)	24(57.1%)	11(55%)	16.1%(-10.1%,42.2%)	2.1%(-24.3%,28.6%)
Any Severe AE	26(68.4%)	30(71.4%)	12(60%)	8.4%(-17.6%,34.5%)	11.4%(-14%,36.9%)
Any Ocular Severe AE	18(47.4%)	19(45.2%)	10(50%)	-2.6%(-29.7%,24.4%)	-4.8%(-31.3%,21.8%)
Any IOP Related AE	17(44.7%)	20(47.6%)	5(25%)	19.7%(-5%,44.4%)	22.6%(-1.6%,46.9%)
≥10 mm Hg IOP Change from Baseline at any visit	17(44.7%)	18(42.9%)	4(20%)	24.7%(1.1%,48.3%)	22.9%(-0.2%,45.9%)
≥25 mm Hg IOP at any visit	18(47.4%)	19(45.2%)	4(20%)	27.4%(3.7%,51%)	25.2%(2.1%,48.3%)
≥30 mm Hg IOP at any	12(31.6%)	13(31%)	3(15%)	16.6%(-4.9%,38.1%)	16%(-5%,36.9%)

visit					
Glaucoma	4(10.5%)	6(14.3%)	2(10%)	0.5%(-15.8%,16.9%)	4.3%(-12.6%,21.2%)
IOP Lowering Procedures	3(7.9%)	3(7.1%)	1(5%)	2.9%(-9.9%,15.7%)	2.1%(-10.2%,14.5%)
	17(44.7%)	20(47.6%)	5(25%)	19.7%(-5%,44.4%)	22.6%(-1.6%,46.9%)
Trabeluctomy	2(5.3%)			5.3%(-1.8%,12.4%)	5.6%(3.3%,7.9%)
Any Cataract Related AE Baseline Phakic Subjects	27(90%)	24(77.4%)	6(54.5%)	35.5%(4.1%,66.8%)	22.9%(-10%,55.8%)
Cataract Surgery in Baseline Phakic Subjects	22(73.3%)	17(54.8%)	3(27.3%)	46.1%(15.4%,76.8%)	27.6%(-4%,59.2%)
Death	3(7.9%)	3(7.1%)	1(5%)	2.9%(-9.9%,15.7%)	2.1%(-10.2%,14.5%)

Source: Reviewer's analysis. Cataract related AE (cataract, cataract nuclear, cataract subcapsular, cataract cortical, cataract diabetic, and lenticular opacities). IOP related AE (IOP increased, ocular hypertension). Glaucoma (absolute glaucoma, ghost cell glaucoma, glaucoma neovascular, secondary glaucoma, secondary open angle glaucoma). All ocular AEs are for the study Eye. Subjects who received at least one study treatment were included and subjects were analyzed according to the treatment they received.

Table 28: Summary of time-to-first IOP-Related AE

Time to First Elevated IOP Related AE	Study A			Study B		
	Treatment: N (%)			Treatment: N (%)		
	0.5 µg/day N=195	0.2 µg/day N=190	Sham N=95	0.5 µg/day N=198	0.2 µg/day N=185	Sham N=90
≤Month 6	50(25.6%)	46(24.2%)	5(5.3%)	44(22.2%)	28(15.1%)	6(6.7%)
> Month 6 ≤ Month 12	28(14.4%)	10(5.3%)	2(2.1%)	16(8.1%)	12(6.5%)	3(3.3%)
Month 15	6(3.1%)	6(3.2%)	1(1.1%)	7(3.5%)	3(1.6%)	1(1.1%)
Month 18	5(2.6%)	3(1.6%)	0(0.0%)	6(3%)	2(1.1%)	0(0.0%)
Month 21	2(1%)	7(3.7%)	0(0.0%)	1(0.5%)	5(2.7%)	1(1.1%)
Month 24	2(1%)	1(0.5%)	0(0.0%)	2(1%)	0(0.0%)	0(0.0%)
Month 27	1(0.5%)	2(1.1%)	0(0.0%)	2(1%)	1(0.5%)	1(1.1%)
Month 30	1(0.5%)	0(0.0%)	0(0.0%)	4(2%)	1(0.5%)	0(0.0%)
Month 33	1(0.5%)	3(1.6%)	0(0.0%)	1(0.5%)	4(2.2%)	0(0.0%)
Month 36	0(0.0%)	2(1.1%)	1(1.1%)	0(0.0%)	3(1.6%)	1(1.1%)
Mean Median Range	9 (7) 6 3, 12	10 (10) 6 2, 15	10 (9) 6 3, 12	9 (9) 6 2, 15	12 (10) 9 6, 15	12 (10) 9 6, 15

Source: Reviewer's analysis. This is the first time a subject reported cataract related AE. Note subjects report more than one cataract related AE.

Table 29: Cross-tabulation of Cataract –related AE and IOP-related AE

IOP AE	Cataract AE: Yes			Cataract AE: No		
	0.5 µg/day	0.2 µg/day	Sham	0.5 µg/day	0.2 µg/day	Sham
Yes	107(27.2%)	72(19.2%)	7(1.9%)	72(18.3%)	67(17.9%)	15(4.0%)
No	128(32.6%)	120(32.0%)	54(14.4%)	86(21.9%)	116(30.9%)	109(29.1%)

Source: Reviewer's analysis.

Table 30: Summary of Subjects who had Cataract surgery among baseline Phakic subjects who reported Cataract AE

Cataract surgery	Study A			Study B		
	0.5 µg/day N=115	0.2 µg/day N=102	Sham N=33	0.5 µg/day N=120	02 µg/day N=90	Sham N=28
Yes	109(94.8%)	94(92.2%)	14(42.4%)	115(95.8%)	83(92.2%)	15(53.6%)
No	6(5.2%)	8(7.8%)	19(57.6%)	5(4.2%)	7(7.8%)	13(46.4%)

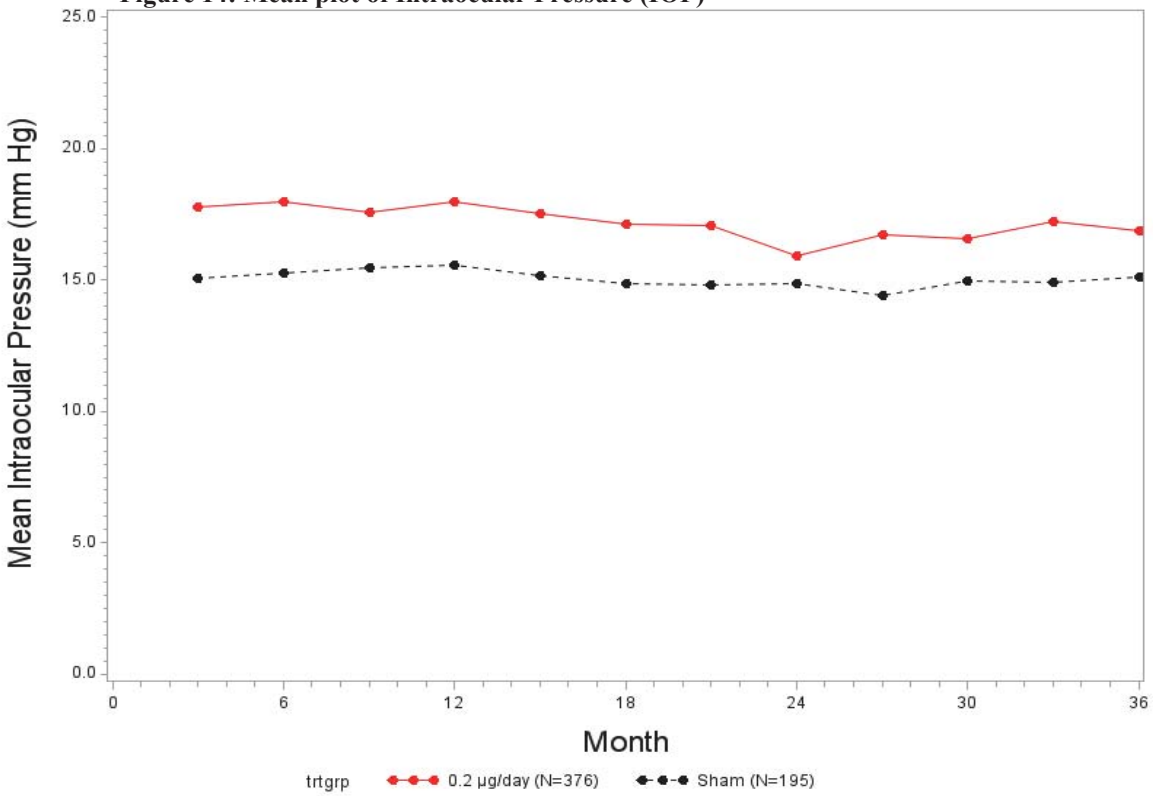
Source: Reviewer's analysis.

Table 31: Summary of time (Month) between first reported Cataract related AE and Surgery

Treatment	Study A		Study B		Pooled	
	Mean (Std)	Median	Mean (Std)	Median	Mean (Std)	Median
0.5 µg/day	3.9(5.2)	3	5.3(5.7)	3	4.6(5.5)	3
0.2 µg/day	4.6(5.1)	3	4.5(5.8)	3	4.6(5.4)	3
Sham	1.2(4.3)	3	4.5(6.5)	3	2.9(5.7)	3

Source: Reviewer's Analysis.

Figure 14: Mean plot of Intraocular Pressure (IOP)



Source: Reviewer's analysis.

APPENDIX D: ADDITIONAL RISK-BENEFIT SUMMARY

Table 32: Summary of Risk-Benefit Analysis (Safety Population) at Month 24

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		0.2 µg/day N=375	Sham N=185	0.2 µg/day N=375	Sham N=185	0.2 µg/day N=375	Sham N=185	0.2 µg/day N=375	Sham N=185
BCVA improvement of ≥15 letters	Any AE	3(0.8%)	3(1.6%)	260(69.3%)	144(77.8%)	105(28%)	27(14.6%)	7(1.9%)	11(5.9%)
	Any Ocular AE	14(3.7%)	11(5.9%)	230(61.3%)	112(60.5%)	94(25.1%)	19(10.3%)	37(9.9%)	43(23.2%)
	Any Serious AE	41(10.9%)	21(11.4%)	119(31.7%)	33(17.8%)	67(17.9%)	9(4.9%)	148(39.5%)	122(65.9%)
	Any Ocular Serious AE	27(7.2%)	14(7.6%)	185(49.3%)	75(40.5%)	81(21.6%)	16(8.6%)	82(21.9%)	80(43.2%)
	Any Severe AE	79(21.1%)	23(12.4%)	77(20.5%)	20(10.8%)	29(7.7%)	7(3.8%)	190(50.7%)	135(73%)
	Any Severe Ocular AE	57(15.2%)	20(10.8%)	142(37.9%)	63(34.1%)	51(13.6%)	10(5.4%)	125(33.3%)	92(49.7%)
	Any IOP Related AE	75(20%)	28(15.1%)	90(24%)	17(9.2%)	33(8.8%)	2(1.1%)	177(47.2%)	138(74.6%)
	≥10 mm Hg IOP Change from Baseline at any visit	76(20.3%)	28(15.1%)	78(20.8%)	10(5.4%)	32(8.5%)	2(1.1%)	189(50.4%)	145(78.4%)
	≥25 mm Hg IOP at any visit	78(20.8%)	28(15.1%)	82(21.9%)	16(8.6%)	30(8%)	2(1.1%)	185(49.3%)	139(75.1%)
	≥35 mm Hg IOP at any visit	85(22.7%)	29(15.7%)	44(11.7%)	4(2.2%)	23(6.1%)	1(0.5%)	223(59.5%)	151(81.6%)
	Cataract Surgery in Phakic Subjects	2(0.9%)	7(6.9%)	104(46.8%)	19(18.6%)	65(29.3%)	9(8.8%)	51(23%)	67(65.7%)
	Cataract related AE in Phakic Subjects	8(3.6%)	3(2.9%)	128(57.7%)	39(38.2%)	59(26.6%)	13(12.7%)	27(12.2%)	47(46.1%)
BCVA improvement of ≥10 letters	Any AE	5(1.3%)	4(2.2%)	226(60.3%)	126(68.1%)	139(37.1%)	45(24.3%)	5(1.3%)	10(5.4%)
	Any Ocular AE	22(5.9%)	16(8.6%)	202(53.9%)	98(53%)	122(32.5%)	33(17.8%)	29(7.7%)	38(20.5%)
	Any Serious AE	63(16.8%)	36(19.5%)	105(28%)	29(15.7%)	81(21.6%)	13(7%)	126(33.6%)	107(57.8%)
	Any Ocular Serious AE	40(10.7%)	24(13%)	162(43.2%)	66(35.7%)	104(27.7%)	25(13.5%)	69(18.4%)	70(37.8%)
	Any Severe AE	106(28.3%)	42(22.7%)	68(18.1%)	20(10.8%)	38(10.1%)	7(3.8%)	163(43.5%)	116(62.7%)
	Any Severe Ocular AE	76(20.3%)	31(16.8%)	125(33.3%)	55(29.7%)	68(18.1%)	18(9.7%)	106(28.3%)	81(43.8%)
	Any IOP Related AE	101(26.9%)	46(24.9%)	80(21.3%)	16(8.6%)	43(11.5%)	3(1.6%)	151(40.3%)	120(64.9%)
	≥10 mm Hg IOP Change from Baseline at any visit	106(28.3%)	46(24.9%)	72(19.2%)	9(4.9%)	38(10.1%)	3(1.6%)	159(42.4%)	127(68.6%)
	≥25 mm Hg IOP at any visit	107(28.5%)	46(24.9%)	75(20%)	15(8.1%)	37(9.9%)	3(1.6%)	156(41.6%)	121(65.4%)
	≥35 mm Hg IOP at any visit	118(31.5%)	48(25.9%)	41(10.9%)	4(2.2%)	26(6.9%)	1(0.5%)	190(50.7%)	132(71.4%)
	Cataract Surgery in Phakic Subjects	6(2.7%)	14(13.7%)	92(41.4%)	15(14.7%)	77(34.7%)	13(12.7%)	47(21.2%)	60(58.8%)
	Cataract related AE in Phakic Subjects	13(5.9%)	8(7.8%)	117(52.7%)	33(32.4%)	70(31.5%)	19(18.6%)	22(9.9%)	42(41.2%)

Summary of Risk-Benefit Analysis at Month 24 (Continued)

Benefit	Risk	Differences: 0.2 µg/day- Sham (95% CI)			
		Benefit + No Risk (Best Case Scenario)	No Benefit + Risk (Worst Case Scenario)	Benefit + Risk	No Benefit + No Risk
BCVA improvement of ≥15 letters	Any AE	-0.8%(-2.9%, 1.2%)	-8.5%(-16.1%, -0.9%)	13.4%(6.6%, 20.2%)	-4.1%(-7.8%, -0.4%)
	Any Ocular AE	-2.2%(-6.1%, 1.7%)	0.8%(-7.8%, 9.4%)	14.8%(8.6%, 21%)	-13.4%(-20.2%, -6.6%)
	Any Ocular Serious AE	-0.4%(-6%, 5.1%)	13.9%(6.6%, 21.1%)	13%(8%, 18%)	-26.5%(-34.9%, -18%)
	Any Ocular Serious AE	-0.4%(-5%, 4.3%)	8.8%(0.1%, 17.5%)	13%(7.1%, 18.8%)	-21.4%(-29.7%, -13.1%)
	Any Severe AE	8.6%(2.3%, 14.9%)	9.7%(3.7%, 15.8%)	3.9%(0.1%, 7.8%)	-22.3%(-30.5%, -14.1%)
	Any Ocular Severe AE	4.4%(-1.4%, 10.2%)	3.8%(-4.6%, 12.2%)	8.2%(3.4%, 13%)	-16.4%(-25%, -7.8%)
	Any IOP Related AE	4.9%(-1.7%, 11.4%)	14.8%(8.8%, 20.8%)	7.7%(4.5%, 11%)	-27.4%(-35.4%, -19.3%)
	≥10 mm Hg IOP Change from Baseline at any visit	5.1%(-1.4%, 11.7%)	15.4%(10.2%, 20.6%)	7.5%(4.3%, 10.6%)	-28%(-35.8%, -20.2%)
	≥25 mm Hg IOP at any visit	5.7%(-0.9%, 12.3%)	13.2%(7.4%, 19%)	6.9%(3.8%, 10%)	-25.8%(-33.8%, -17.8%)
	≥30 mm Hg IOP at any visit	7%(0.3%, 13.7%)	9.6%(5.7%, 13.4%)	5.6%(2.9%, 8.2%)	-22.2%(-29.6%, -14.7%)
	Cataract Surgery in Phakic Subjects	-6%(-11%, -0.9%)	28.2%(18.2%, 38.2%)	20.5%(12.3%, 28.6%)	-42.7%(-53.5%, -32%)
BCVA improvement of ≥10 letters	Any AE	-0.8%(-3.2%, 1.6%)	-7.8%(-16.2%, 0.5%)	12.7%(4.9%, 20.6%)	-4.1%(-7.5%, -0.6%)
	Any Ocular AE	-2.8%(-7.5%, 1.9%)	0.9%(-7.9%, 9.7%)	14.7%(7.4%, 22%)	-12.8%(-19.2%, -6.4%)
	Any Ocular Serious AE	-2.7%(-9.5%, 4.2%)	12.3%(5.4%, 19.3%)	14.6%(9%, 20.1%)	-24.2%(-32.8%, -15.7%)
	Any Ocular Serious AE	-2.3%(-8.1%, 3.5%)	7.5%(-1%, 16.1%)	14.2%(7.5%, 20.9%)	-19.4%(-27.5%, -11.4%)
	Any Severe AE	5.6%(-2%, 13.1%)	7.3%(1.4%, 13.3%)	6.3%(2.2%, 10.5%)	-19.2%(-27.8%, -10.6%)
	Any Ocular Severe AE	3.5%(-3.2%, 10.3%)	3.6%(-4.5%, 11.7%)	8.4%(2.6%, 14.2%)	-15.5%(-24%, -7%)
	Any IOP Related AE	2.1%(-5.6%, 9.7%)	12.7%(6.9%, 18.5%)	9.8%(6.1%, 13.5%)	-24.6%(-33.1%, -16.1%)
	≥10 mm Hg IOP Change from Baseline at any visit	3.4%(-4.3%, 11.1%)	14.3%(9.3%, 19.4%)	8.5%(5%, 12.1%)	-26.2%(-34.6%, -17.9%)
	≥25 mm Hg IOP at any visit	3.7%(-4.1%, 11.4%)	11.9%(6.2%, 17.5%)	8.2%(4.7%, 11.8%)	-23.8%(-32.3%, -15.3%)
	≥30 mm Hg IOP at any visit	5.5%(-2.4%, 13.4%)	8.8%(5%, 12.6%)	6.4%(3.6%, 9.2%)	-20.7%(-28.9%, -12.4%)
	Cataract Surgery in Phakic Subjects	-11%(-18%, -4%)	26.7%(17.3%, 36.2%)	21.9%(12.9%, 30.9%)	-37.7%(-48.6%, -26.7%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values.

Table 33: Summary of Risk-Benefit Analysis (Safety Population) at Month

(b) (4)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized

Summary of Risk-Benefit Analysis at Month [redacted] Continued)

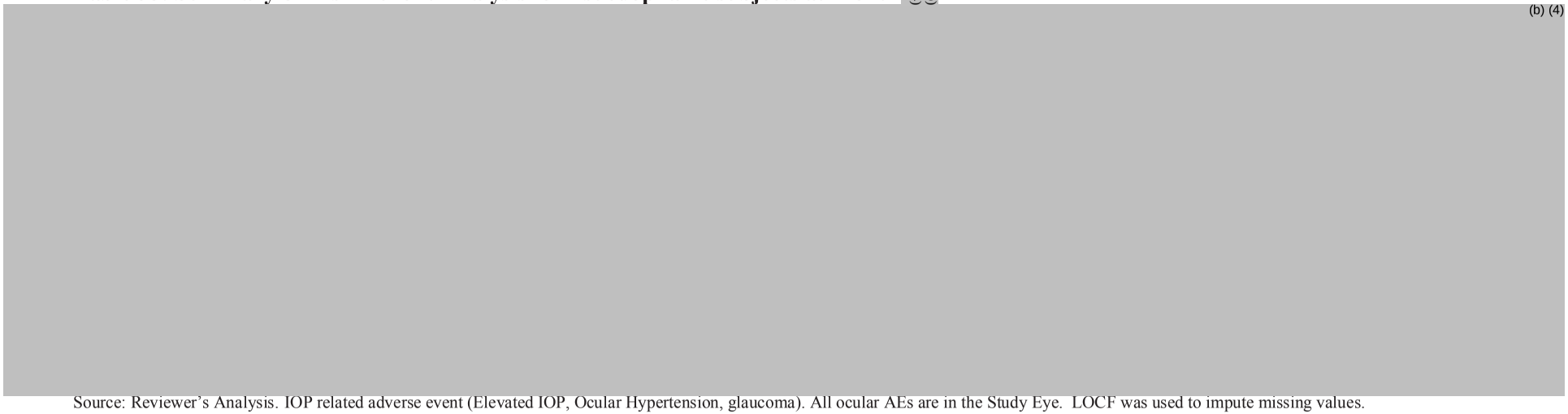
Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values.

Table 34: Summary of Risk-Benefit Analysis for Psuedophakic subjects at Month 24

Benefit	Risk	Benefit + No Risk (Best Case Scenario)		No Benefit + Risk (Worst Case Scenario)		Benefit + Risk		No Benefit + No Risk	
		0.2 µg/day N=140	Sham N=64	0.2 µg/day N=140	Sham N=64	0.2 µg/day N=140	Sham N=64	0.2 µg/day N=140	Sham N=64
BCVA improvement of ≥15 letters	Any AE	3(2%)	3(3.6%)	105(68.6%)	58(69.9%)	38(24.8%)	11(13.3%)	7(4.6%)	11(13.3%)
	Any Ocular AE	13(8.5%)	10(12%)	83(54.2%)	35(42.2%)	28(18.3%)	4(4.8%)	29(19%)	34(41%)
	Any Serious AE	39(25.5%)	14(16.9%)	11(7.2%)	8(9.6%)	2(1.3%)	0(0%)	101(66%)	61(73.5%)
	Any Ocular Serious AE	26(17%)	12(14.5%)	52(34%)	21(25.3%)	15(9.8%)	2(2.4%)	60(39.2%)	48(57.8%)
	Any Severe AE	40(26.1%)	12(14.5%)	11(7.2%)	8(9.6%)	1(0.7%)	2(2.4%)	101(66%)	61(73.5%)
	Any Severe Ocular AE	30(19.6%)	11(13.3%)	42(27.5%)	21(25.3%)	11(7.2%)	3(3.6%)	70(45.8%)	48(57.8%)
	Any IOP Related AE	30(19.6%)	14(16.9%)	39(25.5%)	8(9.6%)	11(7.2%)	0(0%)	73(47.7%)	61(73.5%)
	≥10 mm Hg IOP Change from Baseline at any visit	31(20.3%)	14(16.9%)	37(24.2%)	4(4.8%)	10(6.5%)	0(0%)	75(49%)	65(78.3%)
	≥25 mm Hg IOP at any visit	32(20.9%)	14(16.9%)	36(23.5%)	9(10.8%)	9(5.9%)	0(0%)	76(49.7%)	60(72.3%)
	≥30 mm Hg IOP at any visit	35(22.9%)	14(16.9%)	21(13.7%)	3(3.6%)	6(3.9%)	0(0%)	91(59.5%)	66(79.5%)

Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values.

Table 35: Summary of Risk-Benefit Analysis for Psuedophakic subjects at Month (b) (4)



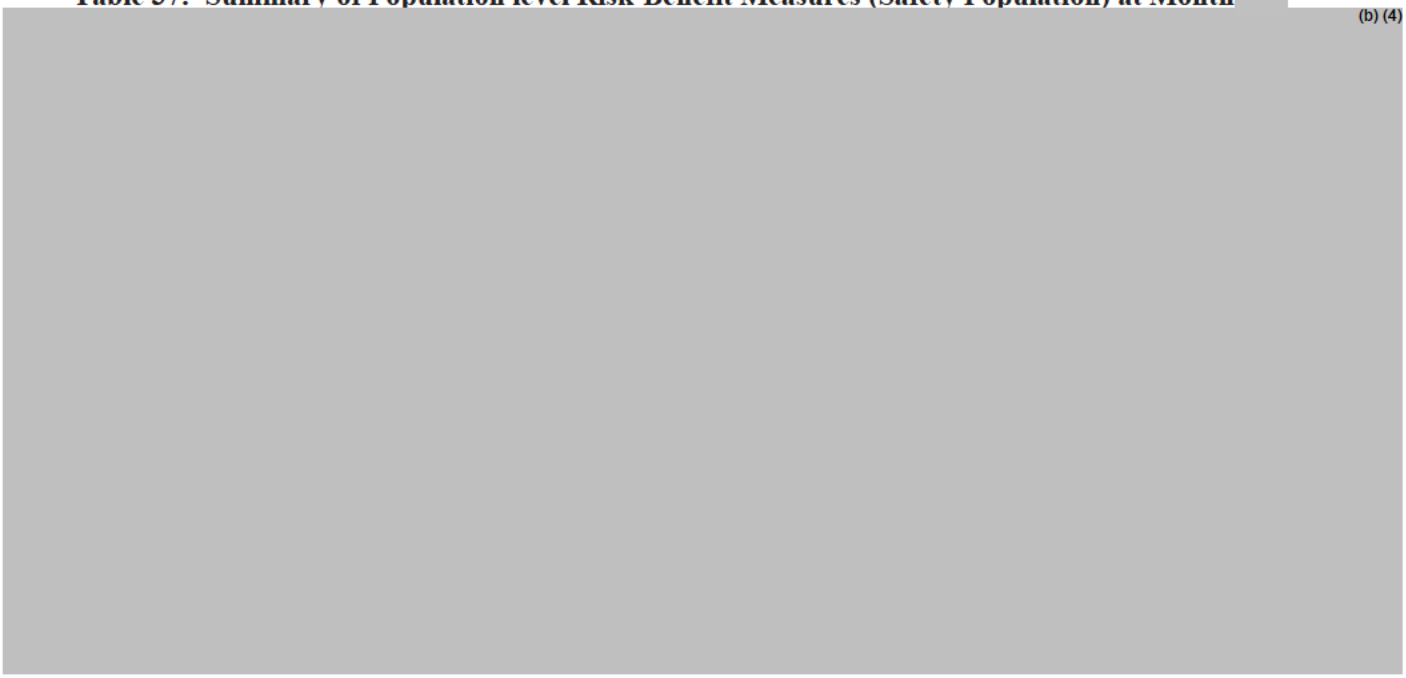
Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). All ocular AEs are in the Study Eye. LOCF was used to impute missing values.

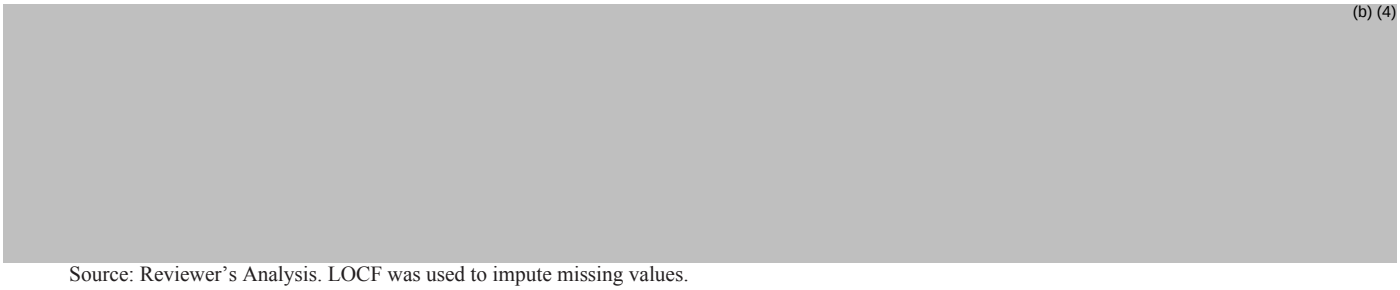
Table 36: Summary of Population level Risk-Benefit Measures (Safety Population) at Month 24

Benefit	Risk	Estimates (95% CI)			
		NNT	NNTadj	NNH	BRR
BCVA improvement of ≥15 letters	Any AE	7.9(5.1,18)	8.4(5.6,18.1)	20.4(11.1,132.3)	2.57(7.37,2.17)
	Any Ocular AE	7.9(5.1,18)	9.4(6.6,19.6)	6.4(4.3,12.2)	0.81(0.68,0.85)
	Any Serious AE	7.9(5.1,18)	10.9(7.8,22.2)	3.7(2.9,5.3)	0.47(0.29,0.56)
	Any Ocular Serious AE	7.9(5.1,18)	10.2(7.3,20.7)	4.6(3.3,7.6)	0.58(0.42,0.65)
	Any Severe AE	7.9(5.1,18)	9.2(6.4,19.3)	7.3(4.9,14.6)	0.92(0.81,0.96)
	Any Ocular Severe AE	7.9(5.1,18)	9(6.4,18.6)	8.3(4.8,30)	1.05(1.67,0.95)
	Any IOP Related AE	7.9(5.1,18)	10.3(7.2,21.4)	4.4(3.4,6.2)	0.56(0.35,0.68)
	≥10 mm Hg IOP Change from Baseline at any visit	7.9(5.1,18)	10.3(7.2,21.6)	4.4(3.5,5.9)	0.55(0.33,0.68)
	≥25 mm Hg IOP at any visit	7.9(5.1,18)	10(6.9,20.8)	5(3.8,7.2)	0.62(0.4,0.74)
	≥35 mm Hg IOP at any visit	7.9(5.1,18)	9.4(6.4,20.1)	6.6(5.1,9.4)	0.83(0.52,1)
	Cataract Surgery in Phakic Subjects	6.9(4.2,19.2)	13.4(10.3,31.2)	2.1(1.7,2.6)	0.3(0.14,0.4)
BCVA improvement of ≥10 letters	Any AE	8.4(5,25.8)	8.8(5.5,26)	20.4(11.1,132.3)	2.43(5.12,2.21)
	Any Ocular AE	8.4(5,25.8)	9.9(6.5,28.1)	6.4(4.3,12.2)	0.76(0.47,0.87)
	Any Ocular Serious AE	8.4(5,25.8)	11.5(7.7,31.9)	3.7(2.9,5.3)	0.44(0.2,0.57)
	Any Ocular Serious AE	8.4(5,25.8)	10.7(7.2,29.8)	4.6(3.3,7.6)	0.55(0.29,0.66)
	Any Severe AE	8.4(5,25.8)	9.7(6.3,27.7)	7.3(4.9,14.6)	0.87(0.57,0.97)
	Any Ocular Severe AE	8.4(5,25.8)	9.5(6.3,26.7)	8.3(4.8,30)	0.99(1.16,0.97)
	Any IOP Related AE	8.4(5,25.8)	10.8(7.1,30.8)	4.4(3.4,6.2)	0.53(0.24,0.69)
	≥10 mm Hg IOP Change from Baseline at any visit	8.4(5,25.8)	10.9(7,31.1)	4.4(3.5,5.9)	0.52(0.23,0.7)
	≥25 mm Hg IOP at any visit	8.4(5,25.8)	10.5(6.8,30)	5(3.8,7.2)	0.59(0.28,0.75)
	≥35 mm Hg IOP at any visit	8.4(5,25.8)	9.9(6.2,28.9)	6.6(5.1,9.4)	0.79(0.36,1.01)
	Cataract Surgery in Phakic Subjects	9.2(4.6,402.2)	17.8(11.3,652.5)	2.1(1.7,2.6)	0.22(0.01,0.37)

Source: Reviewer's Analysis. LOCF was used to impute missing values. .

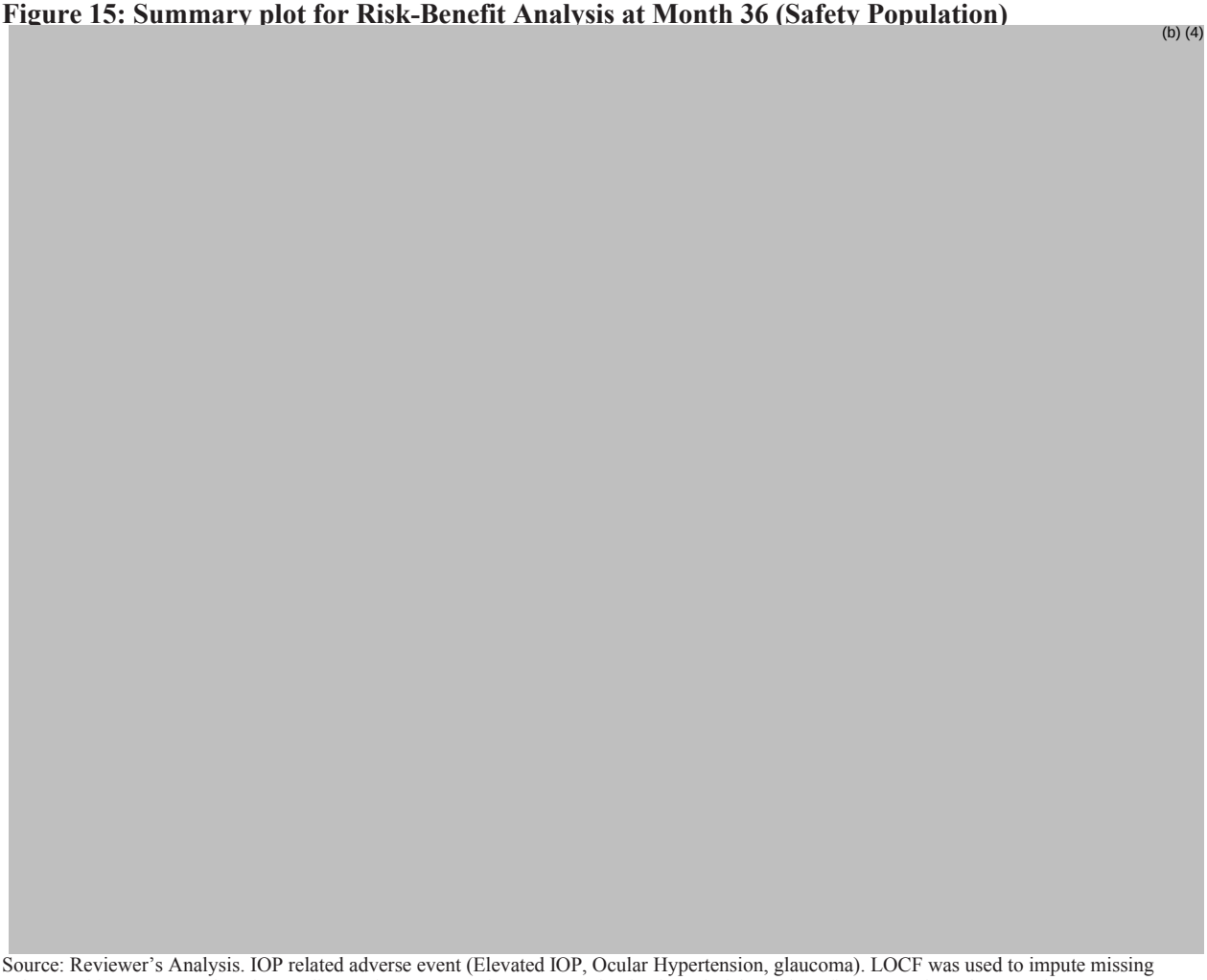
Table 37: Summary of Population level Risk-Benefit Measures (Safety Population) at Month (b) (4)





Source: Reviewer's Analysis. LOCF was used to impute missing values.

Figure 15: Summary plot for Risk-Benefit Analysis at Month 36 (Safety Population)



Source: Reviewer's Analysis. IOP related adverse event (Elevated IOP, Ocular Hypertension, glaucoma). LOCF was used to impute missing values. Subjects were analyzed according to the treatment they were randomized. Both risk and benefit were evaluated at Month 36.

Table 38: Number of subjects with a BCVA measurement by Visit

Visit (Month)	Study A			Study B			Pooled		
	0.5 µg/day N=196	0.2 µg/day N=190	Sham N=95	0.5 µg/day N=199	0.5 µg/day N=186	Sham N=90	0.5 µg/day N=395	0.5 µg/day N=376	Sham N=185
3.0	188(95.9%)	182(95.8%)	94(98.9%)	195(98%)	174(93.5%)	88(97.8%)	383(97%)	356(94.7%)	182(98.4%)
6.0	184(93.9%)	183(96.3%)	91(95.8%)	190(95.5%)	174(93.5%)	83(92.2%)	374(94.7%)	357(94.9%)	174(94.1%)
9.0	172(87.8%)	174(91.6%)	84(88.4%)	181(91%)	165(88.7%)	81(90%)	353(89.4%)	339(90.2%)	165(89.2%)
12.0	175(89.3%)	166(87.4%)	81(85.3%)	178(89.4%)	161(86.6%)	77(85.6%)	353(89.4%)	327(87%)	158(85.4%)
15.0	164(83.7%)	162(85.3%)	83(87.4%)	168(84.4%)	144(77.4%)	68(75.6%)	332(84.1%)	306(81.4%)	151(81.6%)
18.0	154(78.6%)	153(80.5%)	77(81.1%)	155(77.9%)	148(79.6%)	73(81.1%)	309(78.2%)	301(80.1%)	150(81.1%)
21.0	146(74.5%)	148(77.9%)	66(69.5%)	155(77.9%)	143(76.9%)	66(73.3%)	301(76.2%)	291(77.4%)	132(71.4%)
24.0	144(73.5%)	147(77.4%)	70(73.7%)	156(78.4%)	140(75.3%)	64(71.1%)	300(75.9%)	287(76.3%)	134(72.4%)
27.0	143(73%)	144(75.8%)	72(75.8%)	149(74.9%)	133(71.5%)	62(68.9%)	292(73.9%)	277(73.7%)	134(72.4%)
30.0	138(70.4%)	143(75.3%)	67(70.5%)	151(75.9%)	135(72.6%)	61(67.8%)	289(73.2%)	278(73.9%)	128(69.2%)
33.0	125(63.8%)	131(68.9%)	62(65.3%)	143(71.9%)	126(67.7%)	62(68.9%)	268(67.8%)	257(68.4%)	124(67%)
36.0	132(67.3%)	140(73.7%)	67(70.5%)	144(72.4%)	130(69.9%)	59(65.6%)	276(69.9%)	270(71.8%)	126(68.1%)

Source: Reviewer's Analysis

Table 39: Number of who remained in the study by Visit

Visit (Month)	Study A			Study B			Pooled		
	0.5 µg/day N=196	0.2 µg/day N=190	Sham N=95	0.5 µg/day N=199	0.5 µg/day N=186	Sham N=90	0.5 µg/day N=395	0.5 µg/day N=376	Sham N=185
1.0	196(100%)	190(100%)	95(100%)	199(100%)	186(100%)	90(100%)	394(99.7%)	376(100%)	185(100%)
1.5	195(99.5%)	190(100%)	95(100%)	199(100%)	185(99.5%)	90(100%)	393(99.5%)	375(99.7%)	185(100%)
3.0	193(98.5%)	189(99.5%)	95(100%)	198(99.5%)	183(98.4%)	89(98.9%)	391(99%)	372(98.9%)	184(99.5%)
6.0	193(98.5%)	188(98.9%)	95(100%)	197(99%)	179(96.2%)	88(97.8%)	390(98.7%)	367(97.6%)	183(98.9%)
9.0	189(96.4%)	187(98.4%)	92(96.8%)	194(97.5%)	178(95.7%)	88(97.8%)	383(97%)	365(97.1%)	178(96.2%)
12.0	187(95.4%)	181(95.3%)	92(96.8%)	191(96%)	173(93%)	86(95.6%)	378(95.7%)	354(94.1%)	178(96.2%)
15.0	185(94.4%)	181(95.3%)	91(95.8%)	187(94%)	164(88.2%)	85(94.4%)	372(94.2%)	345(91.8%)	176(95.1%)
18.0	178(90.8%)	173(91.1%)	84(88.4%)	183(92%)	160(86%)	81(90%)	361(91.4%)	333(88.6%)	165(89.2%)
21.0	171(87.2%)	170(89.5%)	81(85.3%)	178(89.4%)	157(84.4%)	78(86.7%)	349(88.4%)	327(87%)	159(85.9%)
24.0	161(82.1%)	166(87.4%)	81(85.3%)	175(87.9%)	156(83.9%)	74(82.2%)	336(85.1%)	322(85.6%)	155(83.8%)
27.0	158(80.6%)	161(84.7%)	79(83.2%)	171(85.9%)	153(82.3%)	69(76.7%)	329(83.3%)	314(83.5%)	148(80%)
30.0	154(78.6%)	158(83.2%)	76(80%)	167(83.9%)	150(80.6%)	66(73.3%)	321(81.3%)	308(81.9%)	142(76.8%)
33.0	148(75.5%)	155(81.6%)	73(76.8%)	164(82.4%)	147(79%)	65(72.2%)	312(79%)	302(80.3%)	138(74.6%)
36.0	141(71.9%)	151(79.5%)	73(76.8%)	157(78.9%)	140(75.3%)	64(71.1%)	298(75.4%)	291(77.4%)	137(74.1%)

Source: Reviewer's Analysis. Month 1 indicates a timeframe of 0-3 weeks.

Table 40: Definition of visit Window

Visit Number/ Nominal Visit	Target Day/ Day Range	Visit Number/ Nominal Visit	Target Day/ Day Range
1 / Screening	-21 / < 0	10 / Month 12	360 / 316 – 405
2 / Day 0	0 / 0	11 / Month 15	450 / 406 – 495
3 / Day 1	1 / 1	12 / Month 18	540 / 496 – 585
4 / Week 1	7 / 2 – 14	13 / Month 21	630 / 586 – 675
5 / Week 3	21 / 15 – 31	14 / Month 24	720 / 676 – 765
6 / Week 6	42 / 32 – 66	15 / Month 27	810 / 766 – 855
7 / Month 3	90 / 67 – 135	16 / Month 30	900 / 856 – 945
8 / Month 6	180 / 136 – 225	17 / Month 33	990 / 946 – 1035
9 / Month 9	270 / 226 - 315	18 / Month 36	1080 / 1036 - 1125

Source: From the applicant's submitted report

Table 41: Major Inclusion and Exclusion Criteria

Inclusion/Exclusion criteria

Inclusion criteria:

- Males and non-pregnant females at least 18 years of age
- BCVA of ≥19 and ≤68 letters (20/50 or worse but at least 20/400) by an ETDRS chart. BCVA of the non-study eye must be no worse than 20/400
- Diagnosis of diabetes mellitus (type 1 or type 2). Any one of the following will be considered to be sufficient evidence that diabetes is present:
  - Current regular use of insulin for the treatment of diabetes
  - Current regular use of oral antihyperglycemia agents for the treatment of diabetes
- At least one macular laser treatment more than 12 weeks prior to the screening visit
- DME based on investigator's clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and optical coherence tomography (OCT) despite previous laser treatment
- Mean foveal thickness of at least 250 µm by OCT
- Ability and willingness to comply with the treatment and follow up procedures
- Ability to understand and sign the Informed Consent Form. No expectation that subject will be moving out of the area of the clinical center to an area not covered by another clinical center during the next 36 months.

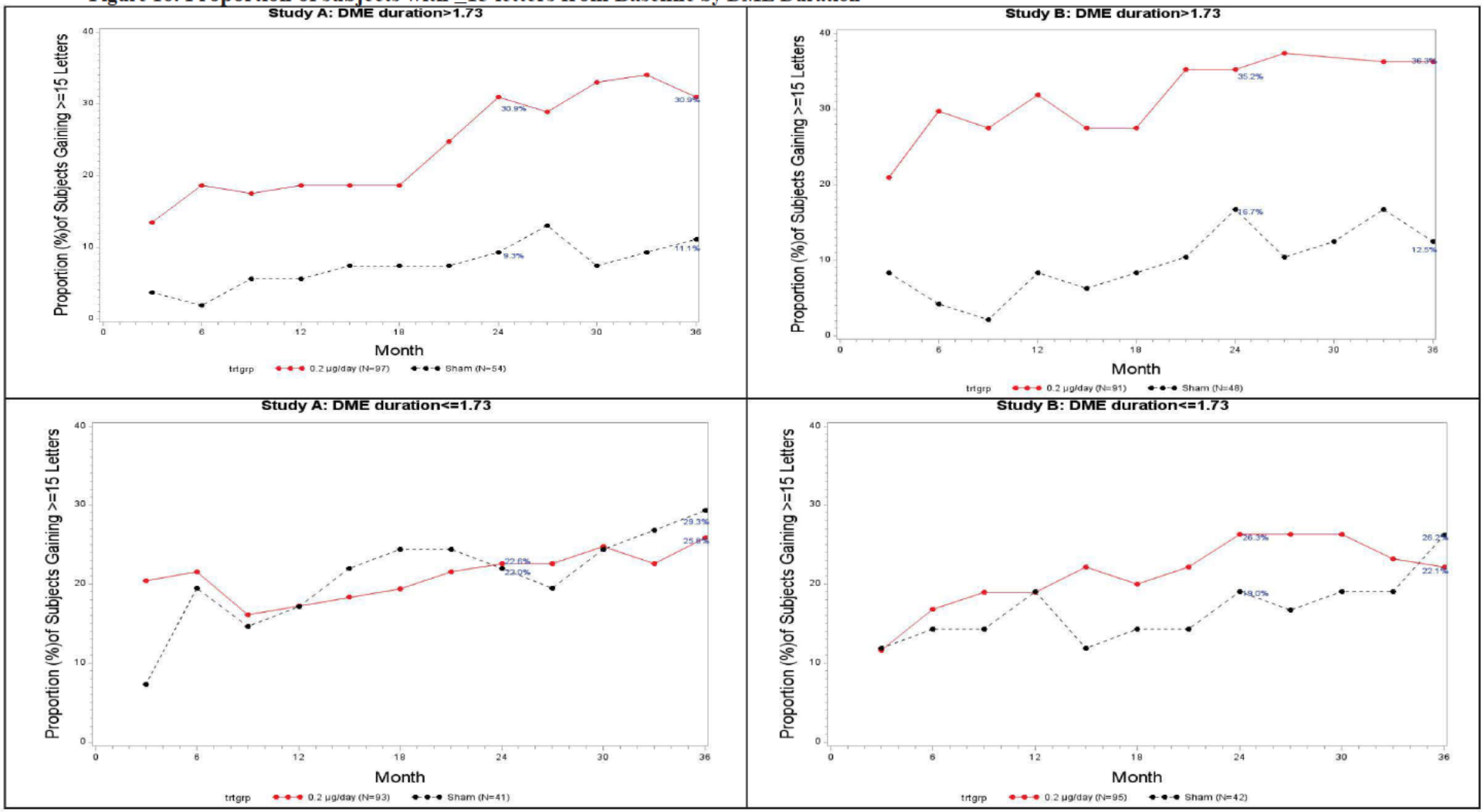
Exclusion criteria:

- Pregnant, lactating females or females of childbearing potential (unless using reliable contraception, i.e. double barrier, surgical sterilization, oral contraceptives, Norplant, intrauterine device (IUD)
- Laser treatment for DME within 12 weeks of screening or judged to be necessary within 6 weeks following enrollment
- Any ocular surgery in the study eye within 12 weeks of screening
- Prior intravitreal steroid therapy within 6 months prior to enrollment (e.g., triamcinolone injection)
- Any change in systemic steroidal therapy within 3 months of screening
- Glaucoma, ocular hypertension, intraocular pressure (IOP) > 21 mmHg or concurrent therapy at screening with IOP-lowering agents in the study eye
- Retinal or choroidal neovascularization due to ocular conditions other than diabetic retinopathy (e.g., presumed ocular histoplasmosis, high myopia (spherical equivalent > 8 diopters), macular degeneration)
- Any viral disease of the cornea or conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, any mycobacterial infections of the eye, any fungal disease of any ocular structure, or history of infectious retinitis
- Known or suspected hypersensitivity to any of the ingredients of the investigational product or to other corticosteroids
- History of vitrectomy in the study eye
- History of IOP elevation with steroid use
- History or presence of any disease or condition (malignancy) that in the investigator's opinion would preclude study treatment or follow-up
- Any lens opacity which impairs visualization of the posterior pole

Source: From the applicant's submitted report

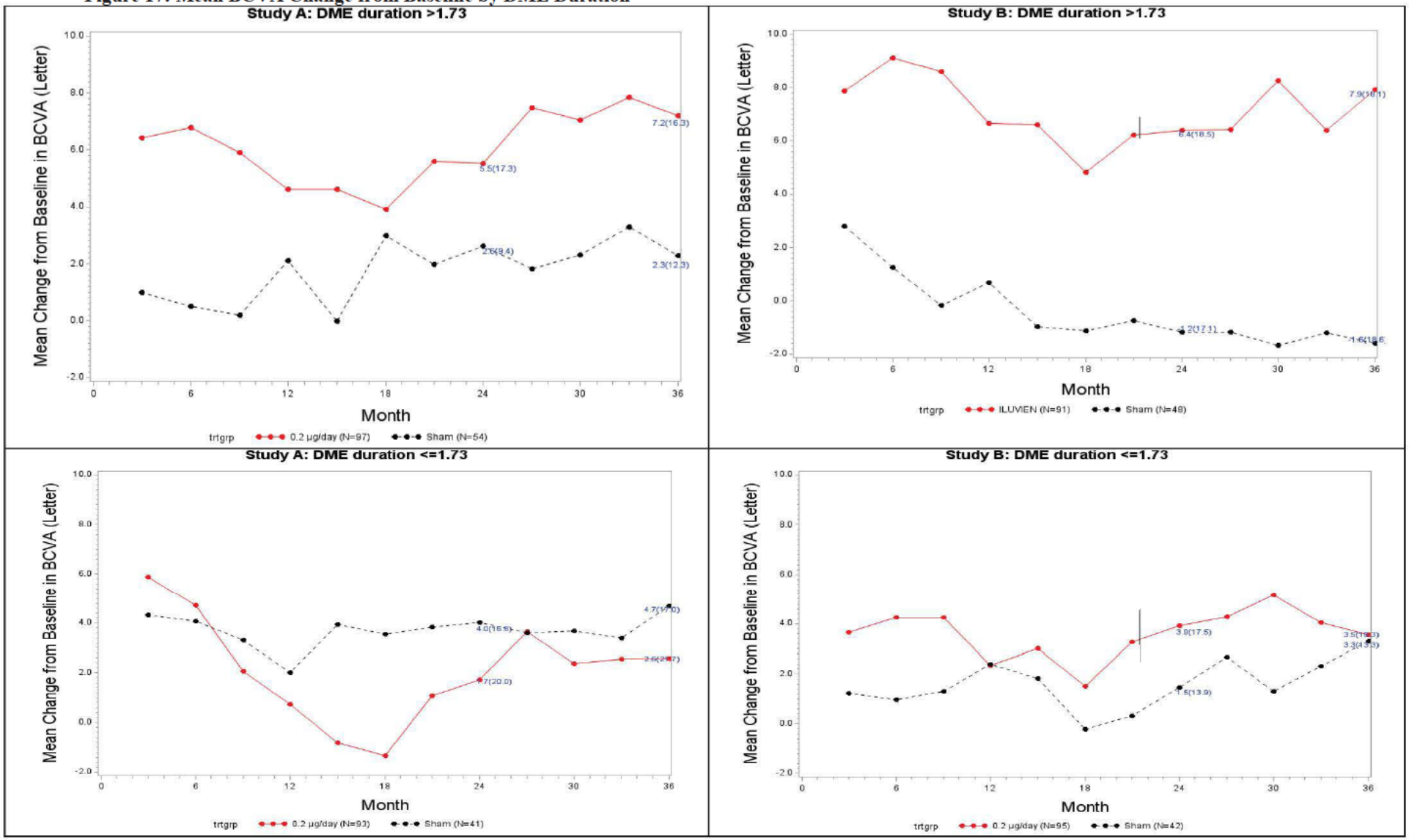
APPENDIX E: ADDITIONAL SUBGROUP ANALYSIS

Figure 16: Proportion of subjects with ≥15 letters from Baseline by DME Duration



Source: Reviewer's Analysis.

Figure 17: Mean BCVA Change from Baseline by DME Duration



Source: Reviewer's Analysis.

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/s/

ABEL T ESHETE
09/02/2014

YAN WANG
09/02/2014
Concur with overall conclusion

NDA Number:	201,923
Serial Number:	0041
SD Number:	0045
Submission Date:	September 9, 2013
Receipt Date:	September 9, 2013
Sponsor:	Alimera Sciences, Inc.
Drug Name:	ILUVIEN® (fluocinolone acctonide intravitreal implant) 0.19 mg
Indication:	(b) (4) Diabetic Macular Edema (DME)

Submission Background

This submission included new analyses of the benefits and risks associated with ILUVIEN for the treatment of (b) (4) DME (b) (4) as a part of major amendment to NDA 201923, which was resubmitted on April 17, 2013 (Serial Number 0036).

Alimera submitted the original NDA for ILUVIEN on June 30, 2010, and on December 22, 2010 Alimera received a Complete Response Letter (CRL) that included efficacy concerns due to the cataract-related effects on visual acuity during months 12-24 and safety concerns related to corticosteroid class events, including IOP elevations and need for cataract removal. FDA requested 36 month data from the FAME studies in order to determine if the benefits of ILUVIEN outweighed the risks after an additional 12 months in the study. On May 12, 2011, Alimera submitted a class 2 response to FDA, which included the requested 36 month safety and efficacy data as well as subgroup analysis. This subgroup analysis showed (b) (4) After its review, the Agency issued second CRL on November 10, 2011. The Agency indicated that results of the clinical program for ILUVIEN did not allow a conclusion that the drug's benefits outweighed its risks.

With this resubmission, Alimera is seeking the approval of ILUVIEN (b) (4) On July 26, 2013, Alimera and its representatives which included two retina specialists and a glaucoma specialist, met with the Agency to understand the outstanding issues regarding NDA 201923 for ILUVIEN. Alimera concluded that there is a significant disconnect between Alimera and the Agency's view of the benefits and risks associated with ILUVIEN (b) (4) for the treatment of DME in general. Alimera is submitting these new analyses to address these opposing views on the risk benefit profile of ILUVIEN.

We present below our review of Alimera's calculation of Number Needed to Treat (NNT) and Number Needed to Harm (NNH) as part of their benefit to risk assessment. It is worth noting that the same analyses were actually included in the Alimera's End of Review Meeting Briefing Package prepared for the June 19, 2012 meeting. The difference is that Alimera only included NNT at Month 30 in this submission.

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[redacted] Summaries of AEs and exposure are included in Appendix for reference, Tables 6-8) [redacted] Therefore, the NNT and NNH that Alimera provided don't offer a fair comparison between NNT and NNH in assessing benefit relative to risk of ILUVIEN. Our calculation of NNH used the same approach for NNT, and the NNH from Alimera's calculation is about 2.8 times of the NNH from our calculation.

Alternatively, NNH from Alimera's calculation can be considered as NNH for one-year period. The NNT for the same one-year period would be [redacted] Therefore, the NNT [redacted] is [redacted] This observation contradicts the Alimera's claim that ILUVIEN offers a positive benefit to risk comparison [redacted]

Conclusion

Alimera's presentation of NNT and NNH didn't offer a fair comparison between NNT and NNH in assessing overall benefit and risk.

Appendix

Table 4: Alimera's Summary of Number (%) of Subjects with a ≥15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) (FAME A)

(b) (4)

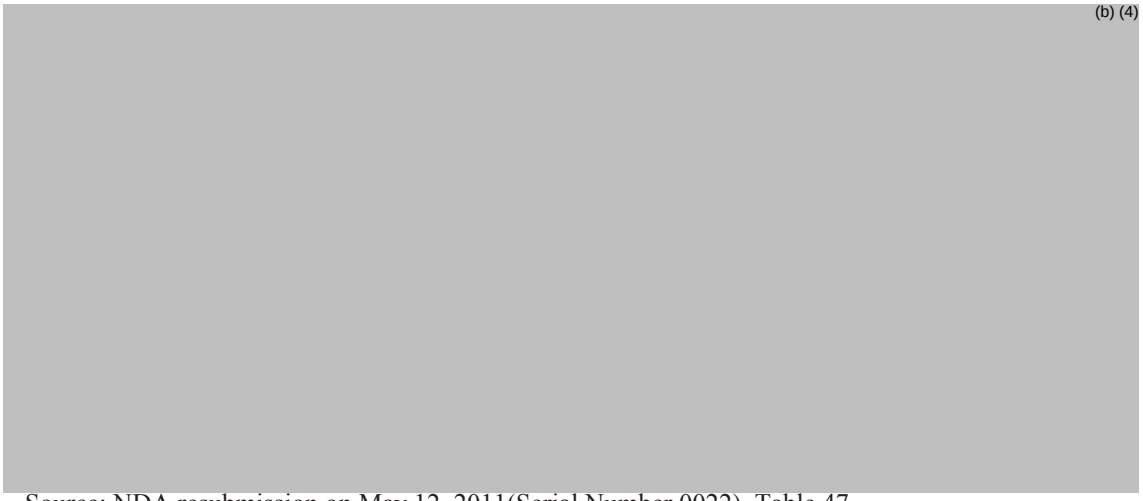
Table 5: Alimera's Summary of Number (%) of Subjects with a ≥15-Letter Increase from Baseline in BCVA in the Study Eye by Duration of DME (b) (4) (FAME B)

(b) (4)

Table 6: Alimera's Summary of Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye for Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)

Source: NDA resubmission on May 12, 2011(Serial Number 0022), Table 46.

Table 7: Alimera's Summary of Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)



Source: NDA resubmission on May 12, 2011(Serial Number 0022), Table 47.

Table 8: Number Needed to Harm for Selected Events (Population: Safety)
Duration of Diabetic Macular Edema (b) (4)

(b) (4)

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/s/

DONGLIANG ZHUANG
09/27/2013

TSAE YUN D LIN
09/27/2013

Type/ Number:	NDA/201,923
Serial Number:	0035
SD Number:	0038
Submission Date:	March 27, 2013
Receipt Date:	March 27, 2013
Sponsor:	Alimera Sciences
Drug Name:	Iluvien® (fluocinolone acetonide intravitreal insert) 0.19 mg
Indication:	(b) (4)

Submission Background

This is a resubmission to the New Drug Application 201,923 in response to the Complete Response letter of 10 November 2011. The original NDA was submitted on June 30, 2010 and received CR letters on December 22, 2010. In response to the CR letter, the Applicant provided a complete response in their May 12, 2011 submission. They received second CR letter on November 11, 2011. A meeting with Alimera was held on June 19, 2012 to discuss what further steps need to be taken in order for this NDA to be approved. This resubmission claims that the recommendations from the CR letter as well as those received during the meeting of 19 Jun 2012 with the Agency, and in the meeting minutes have been incorporated in the resubmission.

The CR letter of 10 November 2011 identified the following deficiencies:

a. Results of your controlled clinical trials C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), did not demonstrate statistically and clinically significant benefit for your primary endpoint of best corrected visual acuity (BCVA) at 36 months. As we have noted previously, efficacy at earlier time points was low (26-(b) (4)% vs. 14-18%), the results were not robust as the difference between groups with respect to mean visual acuity was small and not significant. Although some beneficial effect appeared to occur during the first 6 months, the product then appeared to cause clinically significant decreases in visual acuity at month 24, and was not significantly different from sham treatment by month 36.
b. Results of the safety analyses of your clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. Furthermore, the risk of increased intraocular pressure (IOP) is nearly three times higher in the Iluvien treatment arm than the control arm. The risks of these adverse reactions are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.
c. The to-be-marketed Iluvien Inserter is different from the inserter used is clinical trials, and clinical data from patients treated for diabetic macular edema with the new inserter are not provided in the application. The application only includes data on 8 patients from Study C-01-08-006 who have been enrolled in this study of macular edema in retinal vein occlusion.
d. Your have proposed to revise your indication (b) (4) In support of this revision you have submitted a post-hoc

analysis of the results based on a retrospectively selected subgroup of patients who are said to have duration of DME (b) (4) this analysis was not pre-specified in the protocol, was not included in the statistical analysis plan (SAP), was not adjusted for multiplicity. Furthermore, we note that this subgroup of patients shows the same degree of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population.

To address the clinical and statistical deficiencies, you will need to provide data from two controlled clinical trials that demonstrate that Iluvien, at the dose proposed to be marketed, is safe and effective for the proposed indication you intend to study and seek in labeling. Based on the current trials it appears that neither the 0.2 microgram/day nor 0.5 microgram/day dose is safe and effective, therefore your development program would likely involve new clinical trials, and should include the evaluation of the Iluvien Inserter you propose to market. If these trials are intended to involve patients with diabetic macular edema of (b) (4) duration, you will need to provide specific objective criteria and documentation that subjects had DME continuously (b) (4) because DME is a disease that can wax and wane over the course of many years with varying degrees of macular involvement.

At the June 19, 2012 meeting, Alimera asked the Agency to reconsider the decision of not approving the drug due to its risk-benefit profile. The applicant is still pursuing approval (b) (4) Further, 80% of eyes in phakic patients developed cataracts, up to 40% of patients developed elevated IOP and 5% to 8% had to have surgery to lower their IOP. Therefore, the subgroup of subjects with duration of DME (b) (4) continues to demonstrate the risks associated with the drug. Cataract formation and elevated IOP can lead to decreased vision and a subset of these patients will require additional surgery which introduces additional risks to the patient.

The Agency suggested that if Alimera chooses to provide further analyses based on the data already submitted, it may be beneficial to perform analyses that address qualitative benefits. The applicant could provide a qualitative evaluation of what constituted significant benefit, and include an explanation of why the adverse reactions are not considered to be of particular concern. Any qualitative evaluation should include a

discussion of the risks associated with cataract surgery, the risks associated with IOP elevation and the risks associated with surgical procedures performed for elevated IOP. In summary, the Agency emphasized that based on our interpretations of the results, the risks of cataract development, IOP elevation, and surgery remain a concern for this subgroup of patients.

Alimera will need to explain convincingly why these risks, and the management of them, do not outweigh the observed benefits.

Following the meeting with Alimera, the Agency had the following additional comments for consideration:

1. Regarding surgery for IOP, explain why the surgery used in the treatment of patients enrolled in the clinical trial and its associated risk does not outweigh the benefit shown.
2. Regarding cataract formation and management, explain why the high frequency of development of cataracts and associated surgery is acceptable.
3. Regarding vision, examine the distribution of benefit (15 letters, 20 letters, 25 letters, etc) in the population. If you examine distribution of less than 15 letters, discuss how that represents a clinical benefit.
4. Does removal of the Iluvien insert promptly reverse the adverse events, such as elevated IOP? If so, are there data to support the reversal?

Updates in the Submission

This submission includes the following updates compared to previous submissions.

- Alimera is applying for an indication (b) (4) Therefore, the proposed indication is (b) (4) .
- Alimera argued (b) (4)
- A higher percentage of ILUVIEN-treated patients had BCVA of 20/40 or better at Month 36, providing important functional benefits.
- The benefits of BCVA resulting from ILUVIEN are not limited to a ≥15-letter increase from baseline in BCVA but rather, the benefits can be seen over sham when looking at any change from baseline ranging from ≥0 letters to ≥30 letters.
- The National Eye Institute Visual Function Questionnaire 25 (VFQ-25) was used to assess the impact of ILUVIEN on vision-related quality of life parameters. The

overall difference in mean change in VFQ-25 favored ILUVIEN by approximately 3 points.

- Compared to Lucentis that requires monthly dosing, ILUVIEN provides a reduced treatment burden since a single ILUVIEN implant provides a therapeutic effect for at least 36 months.

Statistical Review Comments:

- This resubmission doesn't include any new efficacy data compared to previous submissions. The new safety data was intended to assess the safety and utility of new applicator of ILUVIEN and therefore, the benefit/risk assessment is unchanged.
- The team determined that this resubmission is not considered a complete response since data tables based on unaudited data in the Interim Safety Report for Study C-01-11-008.

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/s/

DONGLIANG ZHUANG
04/12/2013

YAN WANG
04/12/2013

Statistical Review

NDA: 201923
Document number: 33
Received date: 05/21/2012
Drug: Fluocinolone acetodine intravitreal insert 0.19 mg
Indication: Treatment of Diabetic Macular Edema
Applicant: Alimera Sciences Inc.

Reviewer: Rima Izem
Team leader: Yan Wang

This is a short summary of the meeting package submitted by applicant for the record.

Background:

The original NDA for this drug was submitted in June 28th, 2010 and the FDA issued a complete response (CR) letter in December 12th, 2010.

In response to the CR letter, the applicant submitted additional analyses in May 12th 2011. The FDA issued a CR letter in November 10, 2011 for this second submission.

This meeting package is asking the Agency to reconsider the decision of not approving the drug due to its risk-benefit profile. The applicant is still pursuing approval (b) (4)

The applicant provides more evidence on the choice of the subgroup and its clinical significance. The applicant argues that the subgroup was pre-specified by applicant prior to blinding, although the agency was not notified of the change of the protocol. The applicant also shows analyses to prove consistency of timing of DME given by different physicians.

The applicant reiterates results on this subgroup and shows risk-benefit analyses based on number needed to treat and number needed to harm.

Statistical comments (from internal meetings)

The clinical team has judged that the risk benefit profile of the drug is not favorable, neither in the overall population, nor in the subgroup. The clinical team did not think that the steps outlined by applicant to mitigate the risks of this drug are sufficient.

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/s/

RIMA IZEM
06/20/2012

YAN WANG
06/20/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Supporting document number:	201923/25
Network location	\\Cdsesub1\evsprod\NDA201923\0022
Drug Name:	Iluvien, **Fluocinolone Acetonide Intravitreal Insert 0.19mg**
Indication(s):	Diabetic Macular Edema
Applicant:	**Alimera Sciences Inc.**
Date(s):	Received date: 05/12/2011 PDUFA goal date: 11/12/2011
Review Priority:	Priority
Biometrics Division:	DB 4
Statistical Reviewer:	Rima Izem
Concurring Reviewers:	Yan Wang
Medical Division:	DTOP
Clinical Team:	Clinical Reviewer: Martin Nevitt. Clinical Team Leader: William Boyd.
Project Manager:	Lori Gorski, Raphael Rodriguez

Keywords: Diabetic Macular Edema, Risk-Benefit analysis, Best Corrected Visual Acuity, Responder Analysis, Elevated IOP, Cataract

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1 Executive Summary

This is a statistical review of NDA 201923's re-submission addressing the complete response letter sent to applicant for the original NDA submission. This review supplements the review of the original submission.

The original NDA seeks approval of Iluvien for the treatment of diabetic macular edema (DME). Iluvien is a sustained-release intravitreal drug delivery system that releases submicrogram levels of fluocinolone acetonide (FA), a glucocorticoid, in the vitreous humor for (b) (4) 36 months. There are currently no approved drugs for this indication.

The current submission complements the 24 months data on the two pivotal trials (FAME A and FAME B) in the original NDA by the data up to 36 months data in these two trials. The current submission also shows the results for a subgroup of subjects who have been diagnosed with DME (b) (4) Based on this subgroup analysis, the current submission seeks the following more restricted indication than the original NDA:

(b) (4)

Two doses, 0.2 µg/day FA and 0.5 µg/day FA, were included in the pivotal trials; only the low dose is proposed for the sought indication in both the original and current submissions because the low dose had similar efficacy and better safety than the high dose

The main review issue with the results of this submission is the same as with the original NDA, that is weighing the benefit of Iluvien treatment on improving Best Corrected Visual Acuity (BCVA) against its risks of causing elevated Intra Ocular Pressure (IOP) and cataract formation and surgery. In the following, we summarize the benefit and risks in the general population and in the subgroup presented by applicant. We first summarize the efficacy findings on improving Best Corrected Visual Acuity (BCVA). The efficacy findings include results on the primary endpoint of BCVA increase from baseline above 15 letters and results on the secondary endpoint of mean BCVA change from baseline. We then summarize the safety findings on elevated IOP and cataract surgery. Finally, we give our recommendations based on the risk-benefit findings.

In the overall population and for the primary efficacy endpoint of proportion of subject with improvement of BCVA from baseline of 15 letters or more, low dose is significantly better than sham at Month 24 (b) (4) (see Table 1). At Month 24, the difference between low dose and sham is of 12% in FAME A (p-value = 0.03) and 13% in FAME B (p-value = 0.03). (b) (4)

In the overall population and for the secondary endpoint of mean BCVA change from baseline, low dose is significantly better than sham at Month 24 (b) (4) in FAME B but the effect is not replicated in FAME A at any timepoint (see Figure 1 and Table 8). In FAME B, the treatment effect and 95% confidence interval in lines of vision over time is 5 (0.7, 9.4) at month 24, 7 (2.6, 11.3) (b) (4) In FAME A, the treatment effect and 95% confidence interval in lines of vision over time is 0 (-3.8, 4.6) at month 24, 2 (-2.5, 6.2) (b) (4)

In summary, for the drug efficacy on BCVA in the overall population from month 24 to month 36, the results on primary endpoint and secondary endpoint together with exploratory cumulative distribution function curves in Figure 2 show the following: On one hand, the low dose has a higher proportion of subjects whose vision improves from baseline compared to sham; on the other hand, the low dose has a similar or higher proportion of subjects whose vision declines from baseline compared to sham. Thus, the effect on mean BCVA change from baseline of low dose compared to sham is small and has high variability.

In the overall safety population, the risk of elevated IOP or cataract surgery is three folds higher in the low dose compared the sham. The proportion of subjects with IOP elevation considered an adverse event is 37% in the low dose group compared to 12% in the sham group. The incidence of cataract operation by month 36 in the safety population is 27% in sham arm and 80% in the low dose arm. We note that cataract formation and surgery is a confounder on efficacy since cataract formation and surgery decrease BCVA. Since most subjects in the low dose arm have cataract surgery by month 24, the confounding effect of cataract on BCVA decreases after month 24 (see Figure 3).

The review considered additional exploratory analyses of the composite outcome of benefit and risk at the subject level in the general population with benefit being BCVA change ≥ 15 letters and risk being IOP increase or ocular hypertension or cataract surgery (see Table 6). For either risk outcomes, these analyses are not favorable to the low dose arm.

(b) (4) The overall safety results with respect to IOP elevation and cataract surgery are similar to the general population and are shown in Table 3 and Table 5.

The subgroup of DME (b) (4) was neither a preplanned subgroup in the statistical analysis plan before unblinding of study results, nor was it presented as a special subgroup in the original NDA submission. So, although this subgroup shows a better

safety benefit profile than the general population, the results should be considered with caution as these are all post-hoc analyses and the applicant could have found this subgroup with better risk-benefit profile than the general population simply by chance.

The review finds that the applicant did not demonstrate (b) (4)

In conclusion, we defer to the clinical review to weigh the benefit against the risk of this drug in the general population or in the subgroup of DME (b) (4)

but the drug harms a significantly higher proportion of subjects compared to sham. The two main harms considered here are IOP elevation or cataract surgery. (b) (4)

However, this subgroup was determined post-hoc so any results should be considered with caution. The statistical review cannot weigh the benefit of BCVA gain versus the risk of cataract surgery or elevated IOP and we defer to the clinical review team to weigh these outcomes against each other.

2 Background and Introduction

This is a review of the NDA 201923 resubmission addressing the complete response (CR) letter for the original submission. The NDA is seeking approval of Iluvien for the treatment of diabetic macular edema (DME). Iluvien is a sustained-release intravitreal drug delivery system that releases submicrogram levels of fluocinolone acetonide (FA), a glucocorticoid, in the vitreous humor for (b) (4) 36 months. There are currently no approved drugs for this indication.

The original NDA for this drug was submitted in June 28th, 2010 and the FDA issued a complete response (CR) letter in December 12th, 2010. The applicant met with the FDA in February 2nd, 2011 with questions about the CR letter. This re-submission is in response to the CR letter and requests a different indication.

The main conclusions from the previous review are the following

- Iluvien's main efficacy claim on Best Corrected Visual Acuity (BCVA) at Month 24 is debatable. On one hand, we agree with the applicant that the two pivotal studies met their primary endpoint. That is, the active dose arms have a significantly higher proportion of subjects whose BCVA increase by 15 letters or more from baseline to Month 24 compared to the sham arm. On the other hand, the active dose arms have also a higher proportion of subjects whose BCVA decrease by 15 letters or more from baseline to Month 24 compared to the sham arm.

- The drug induces serious risk of cataract surgery and elevated intra-ocular pressure. The incidence of cataract surgery during the study is significantly higher in the active dose arms compared to the sham arm. The incidence of surgery due to elevated intra-ocular pressure is also higher in the active dose arms compared to the sham arm.

- Three year data is needed to further evaluate the effect of cataract on BCVA. The applicant's and the reviewer's exploratory analyses indicate that the likely cause of BCVA decline is development of cataract. With longer follow up time data from these studies, we can test this causal hypothesis and thus better evaluate the benefit and risk of Iluvien treatment.

The following comments from the statistical review were conveyed to applicant concerning the analysis of three year data:

"In addition to the predetermined analyses in the protocol for the three year data, include the following exploratory analyses:

- Risk-benefit analyses at the study eye level. This could be explored using two way tables of major adverse event (such as cataract surgery) versus improvement of BCVA by 15 letters or more.

- Association of decline of BCVA by 15 letters or more to cataract at the study eye level. This could be explored by checking association of cataract surgery to decline in BCVA by 15 letters or more by visit.

- Sensitivity analyses to missing values. Proposed additional sensitivity analyses are as follows:

1) Treating all missing observations as failures in primary endpoint.
2) Treating all deaths as failures in primary endpoint, and imputing the other missing values using multiple imputation methods.
3) Treating all deaths as failures in primary endpoint, imputing other missing values using multiple imputation methods, and imputing observed values for subjects with disallowed medication using multiple imputation methods.

Confidence intervals for the treatment effect in the last two methods should account for the uncertainty in the imputed values."

3 Main Changes in this Submission Compared to Original Submission

The submission has some material requested by the agency and the statistical reviewer in the CR letter. In addition, the submission has an important change in indication. The current NDA is seeking approval for a more restricted indication than the one sought in the original NDA. The support for this new indication is (b) (4)

The current submission adds the results of the clinical trials between month 24 and month 36 to the results up to month 24 from the previous submission, as requested by the statistical reviewer. In addition, the current submission shows the results of exploratory analyses of risk benefit, association between decline of BCVA and cataract and sensitivity analyses due to missing values requested by the statistician.

One important change in this application compared to the previous submission is the change in indication and primary efficacy population. In the original submission, the indication is for *Treatment of Diabetic Macular Edema (DME)* and the primary efficacy population is the full analysis population (all randomized with last observation carried forward (LOCF) to impute missing values). In the current submission, the indication is for (b) (4)

4 Efficacy in the Overall Study Population, Results from Month 24 to Month 36

This section will discuss the efficacy results for the period between month 24 and month 36 on the full analysis population. This section supplements the statistical review of efficacy in the original submission.

The statistical review of the original submission found the efficacy effect of Iluvien on BCVA in the full analysis population small at month 24. Our review of the additional evidence in this submission still finds the efficacy small at month 24 and between month 24 and month 36.

Efficacy on best corrected visual acuity (BCVA) was evaluated using two endpoints. The primary endpoint is the proportion of subjects with BCVA change from baseline ≥ 15 lines and the secondary endpoint is the mean BCVA change from baseline. The primary analysis population is the full analysis population, that is all randomized subjects using the LOCF imputation method for missing visits.

The primary endpoint is a responder endpoint; it only quantifies improvement from baseline BCVA that is above a threshold of 15 letters. In contrast, the secondary endpoint quantifies any change from baseline, whether they are improvements or declines from baseline BCVA. In all treatment arms, in both studies and at most time-points, some subject's BCVA increased while other subject's BCVA decreased compared to baseline. Thus, the primary and secondary endpoints together give a better picture of the low dose treatment effect and magnitude of the effect on BCVA than the primary endpoint alone.

The primary endpoint is *significant* in the low dose group in both FAME A and FAME B at month 24 (b) (4) at 5% level of significance (see Table 1). That is the proportion of subjects with increase of 15 letters or more is significantly higher in the low dose group than in the sham group at month 24 (b) (4) in both FAME A and FAME B. However, this endpoint is no longer significant by month 36.

Table 1: Number (%) of Subjects with a ≥15-Letter Increase from Baseline in BCVA in the Study Eye (FAME A and FAME B, Full Analysis Population)

Time Point	FAME Study A			FAME Study B		
	Treatment Group			Treatment Group		
	Sham	0.2 µg/day FA	0.5 µg/day FA	Sham	0.2 µg/day FA	0.5 µg/day FA
	N=95	N=190	N=196	N=90	N=186	N=199
Month 18, n (%)						(b) (4)
Difference[1]						
P-value[2]						
Month 24, n (%)	14 (14.7)	51 (26.8)	51 (26.0)	16 (17.8)	57 (30.6)	62 (31.2)
Difference[1]		−12.1	−11.3		−12.9	−13.4
P-value[2]		0.029	0.034		0.030	0.027
Month 30, n (%)						(b) (4)
Difference[1]						
P-value[2]						
Month 36, n (%)						
Difference[1]						
P-value[2]						

[1] Difference is sham minus active. A negative value denotes a higher percentage of subjects in the active group who showed improvement in BCVA.

[2] P-value based on a CMH chi-square test stratified by baseline VA.

Source: Applicant's Table 3 from Efficacy Information Amendment

The secondary endpoint of mean BCVA over time shows a small advantage of low dose over Sham in FAME B but this effect is not replicated in FAME A (see Figure 2 and corresponding Table 8 in Appendix). The difference between low dose and sham is marginally significant from month 24 to month 36 in FAME B. The difference between low dose and sham is not significant in FAME A at all visits after month 6.

Although the primary endpoint seems to show significant improvement in BCVA over time in the low dose compared to sham in FAME A, the effect on the secondary endpoint is not significant in this study. The reason for the difference in the results on the two endpoints in this case is that we have simultaneously (1) the low dose has some advantage over sham in the proportion of subjects whose vision improves from baseline, and (2) the low dose is the same or worse than sham for the proportion of subjects whose vision declines from baseline.

To illustrate the difference between the primary endpoint and secondary endpoint in FAME A, we show the empirical cumulative distribution functions (ecdf) of change of BCVA from baseline in this study in Figure 2. For a given observed value of change from baseline BCVA, the ecdf shows the proportion of subjects with change below this given change from baseline. Thus, the treatment effect of low dose versus sham for the primary endpoint (proportion with change from baseline ≥ 15 letters) is the vertical distance between the blue curve (sham) and the red curve (low dose) along the solid vertical line at +15 letters. Since the low dose curve (red) is lower than the sham curve (blue), it indicates that the proportion of subjects with BCVA change from baseline ≥ 15 letters is higher in the low dose group than sham group.

On one hand, we see in Figure 2 that at month 24, (b) (4) and at different positive thresholds (including the threshold of +15 letters for primary endpoint), the proportion of subjects whose vision improves above these thresholds from baseline is higher in the low dose arm than in the sham arm. This is the case because we see that for all positive values of change from baseline including +15 lines change in the primary endpoint, the low dose arm ecdf is below the sham arm ecdf.

On the other hand, we see in the top subplot at month 24 that at different negative thresholds (including the threshold of -15 letters as safety endpoint), the proportion of subjects whose BCVA declines below that threshold is higher in the low dose arm compared to the sham arm. This is the case because for negative values of change of BCVA from baseline, the low dose arm ecdf is above the sham arm ecdf. We see in the middle and lower subplot that at month 24 (b) (4) the proportion of subjects with decline in BCVA from baseline is similar in the two treatment arms at all negative thresholds (i.e. the two ecdf lines are almost identical at negative value).

Results for FAME B are shown in Figures 9-10 in Appendix. In FAME B, the decline in BCVA from baseline is not as pronounced as in FAME A and the improvement in BCVA from baseline is more pronounced than in FAME A.

Figure 1: BCVA Change From baseline, Treatment Effect of Low dose versus Sham in Full Analysis Population by Visit and Study

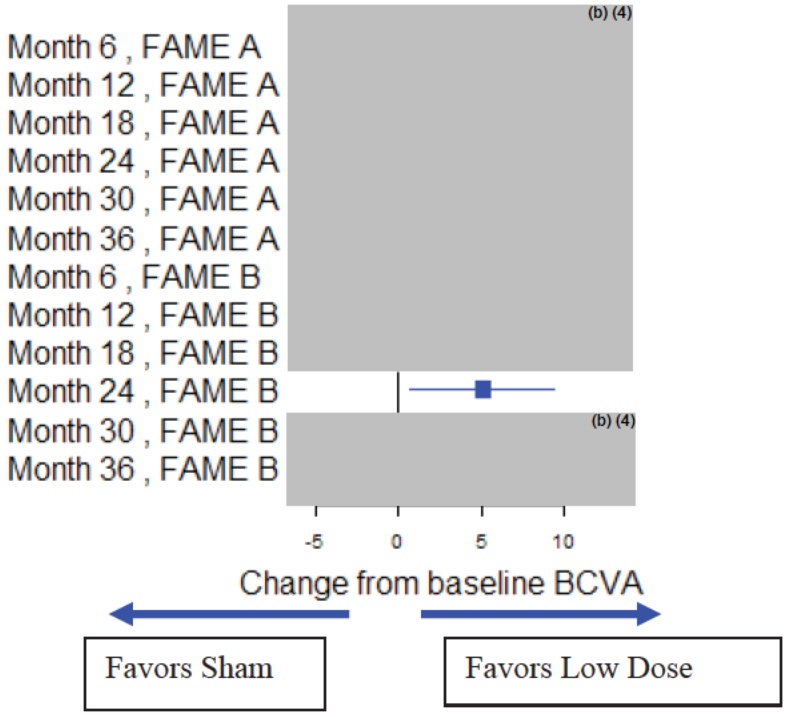
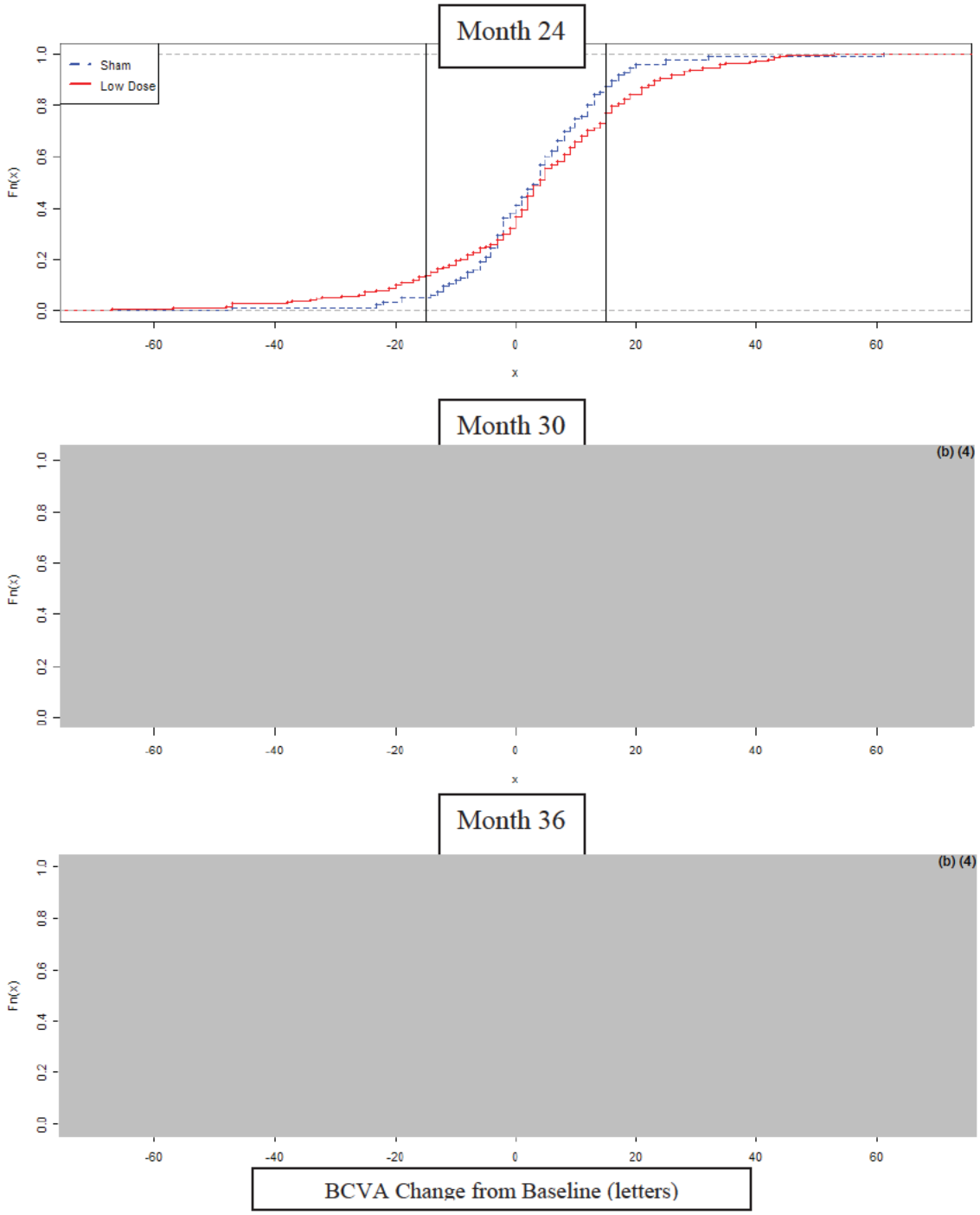


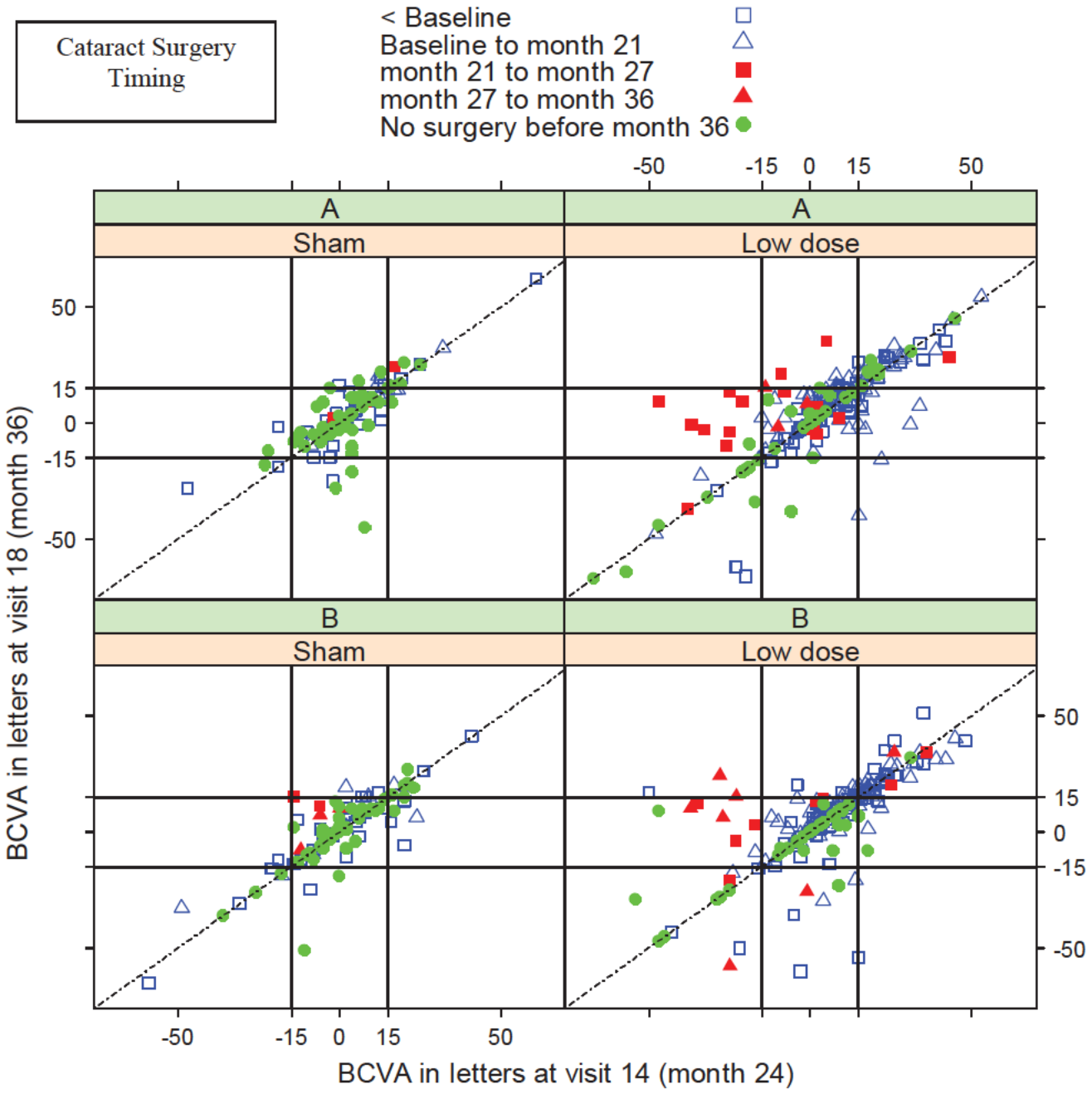
Figure 2: Cumulative Distribution Function of BCVA Change from Baseline at Month 24 (top), Month 30 (middle) and Month 36 (bottom) for FAME A in Full Analysis Population



In the original applicant's submission and our review of the original submission, cataract was found to be a plausible explanation for loss of vision at month 24 in the low dose group (see Figure 2, top panel) based on the BCVA pattern over time up to month 24. Cataract is a known treatment related adverse events to corticosteroids and cataract causes vision loss. After cataract surgery, subjects recover their vision after a few months.

Figure 3 confirms that most of the subjects who lost 15 lines or more of BCVA in the low dose group in both studies (points at the left of the leftmost vertical line) had cataract surgery around month 24 visit (red filled rectangles with surgery between month 21 and month 27). These subjects' BCVA came back to at least baseline level at month 36 (above the lower vertical line). Note that the observations in the lower leftmost quadrant are for those subjects whose vision decline was high in both visits. Most of these observations fall exactly on the 45 degree line which indicates that the month 36 observation is missing and was imputed. So, loss of vision at month 24 in the low dose group is associated to cataract surgery timing. Since most subjects in the low dose arm had cataract surgery by month 24, the confounding effect of cataract and cataract surgery on primary and secondary endpoint seems to lessen after this time.

Figure 3: BCVA Change from Baseline at Month 24 versus Month 36 by Study, Treatment and Cataract Timing, Full Analysis Population



5 Efficacy for DME (b) (4) Subgroup

The applicant is seeking a new indication (b) (4)

The sought indication (b) (4)

did not show evidence (b) (4)

(b) (4)

The list of preplanned subgroups in the statistical Analysis plan does not include DME as a grouping variable and includes 11 preplanned grouping variables. These grouping variables are: demographic variables of Age (<median, ≥median years), Sex (males, females), Race (Caucasians, black/African-American, Asian, others), Iris color (dark (black, brown), light (hazel, green, blue, gray)); geographic variables of Study center and Continent (North America, European Union, India); ocular medical history variables of Lens status (aphakic, pseudophakic, phakic), Total area of cystoid changes at baseline (<median%, ≥median %), Total area of fluorescein leakage at baseline (<median%, ≥median %), Total area of capillary loss at baseline (<median%, ≥median %)); and other medical history variable of Baseline HbA1c (<median%, ≥median %).

(b) (4)

(b) (4)

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6 Risk and Risk Benefit

In this section we briefly summarize the safety issues with Iluvien and quantify the risk benefit at the individual level. We refer to the clinical review for a more extensive discussion on safety and risk benefit.

6.1 Safety in Overall Study Population and Subgroup of DME (b) (4)

The two main treatment-related adverse events are cataract and elevated IOP. As we see in Table 2, elevated IOP was significantly higher in the low dose arm (37%) than in the sham arm (12%). The incidence of surgical intervention related to elevated IOP was also higher in the low dose group (5%) than in the sham group (0.5%).

(b) (4)

Different treatment rates with IOP-lowering medications and procedures may also play a role in the reduction of IOP in the second and third year.

In the subgroup of DME (b) (4) the safety results (b) (4)

Table 2: Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye (36-Month Integrated FAME Studies, Safety Population)

Category	Treatment Group		
	Sham (N = 185) n (%)	0.2 µg/day FA (N = 375) n (%)	0.5 µg/day FA (N = 393) n (%)
IOP elevation considered an AE[1]	22 (11.9)	139 (37.1)	(b) (4)
IOP elevation increase ≥12 mmHg	15 (8.1)	108 (28.8)	
IOP elevation to over >25 mmHg	18 (9.7)	123 (32.8)	
IOP elevation to over >30 mmHg	8 (4.3)	69 (18.4)	
Trabeculoplasty surgery performed	0	5 (1.3)	
Trabeculectomy surgery performed	0	10 (2.7)	
Glaucoma surgery performed[2]	1 (0.5)	8 (2.1)	
Vitrectomy performed for elevated IOP	0	1 (0.3)	
Any surgical intervention	1 (0.5)	18 (4.8)	

1 Includes the following procedures performed for treating elevated IOP: Any surgery for reduction of IOP and vitrectomy performed to remove the study drug.

Source: Applicant's Table 41 from the Efficacy Information Amendment of the current submission

Table 3: Incidence of Intraocular Pressure-Related Events and Procedures in the Study Eye for Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)

(b) (4)

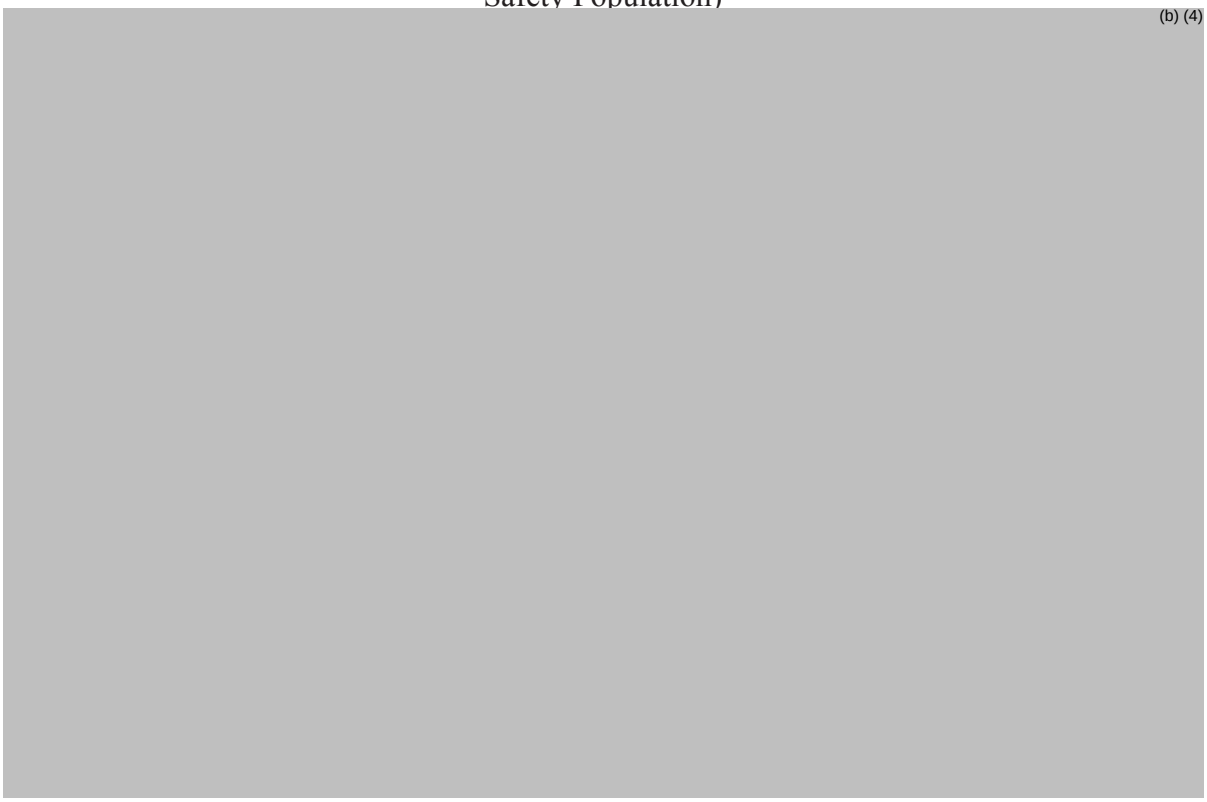

Figure 8: Mean Change from Baseline Intraocular Pressure (SEM) in the Study Eye: Integrated FAME Studies

Source: Applicant's Figure 27 in the Efficacy Information Amendment of the current submission.

Table 4: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects (36-Month Integrated FAME Studies, Safety Population)

Category	Treatment Group		[redacted] (b) (4)
	Sham (N = 121) n (%)	0.2 µg/day FA (N = 235) n (%)	
Any cataract-related AE	61 (50.4)	192 (81.7)	
Cataract NOS	51 (42.1)	168 (71.5)	
Cortical cataract	1 (0.8)	1 (0.4)	
Diabetic cataract	0 (0.0)	1 (0.4)	
Nuclear cataract	5 (4.1)	8 (3.4)	
Subcapsular cataract	8 (6.6)	27 (11.5)	
Cataract operation	33 (27.3)	188 (80.0)	

Source: Applicant's Table 42 from the Efficacy Information Amendment of the current submission

As we see in Table 4, 82% of phakic eyes at baseline have cataract related adverse event by month 36 in the low dose group compared to only 50% in the sham arm. In addition, 80% of the phakic eyes in the low dose group required cataract surgery by month 36 whereas only 27% in the sham arm required surgery. Based on sponsor's results, median time to surgery for cataract removal in phakic subjects was 550 days (18.3 months) in the low dose group.

The results for the subgroup of DME [redacted] (b) (4) for cataract adverse events are [redacted] (b) (4)

Table 5: Incidence of Cataract-Related Events in the Study Eye of Phakic Subjects with a DME Duration (b) (4) (36-Month Integrated FAME Studies, Safety Population)

(b) (4)

Source: Applicant's Table 47 from the Efficacy Information Amendment of the current submission

6.2 Risk-Benefit Assessment at Subject Level

In this section we quantify the risk-benefit trade-off at the subject level. The benefit here is increase BCVA from baseline ≥ 15 letters. The two risks we explore are cataract surgery and increase IOP or ocular hypertension.

When considering the risk of cataract surgery and the benefit of BCVA, the risk-benefit profile of the sham group is better than the low dose group in both the general population and the DME subgroup. As we see in Table 6 for the observed cases in both studies, a significantly larger proportion of subjects in the sham arm have benefit at any time during the study with no cataract surgery (21%) than in the low dose arm (5%). We see also that only 14% of subjects in the sham group have cataract surgery and no benefit at anytime compared to 33% of subjects in the low dose. The subgroup of those with DME (b) (4) as shown in Table 7.

When considering the risk of increase IOP or ocular hypertension and the benefit on BCVA, the risk-benefit profile of the sham group is better than the low dose group in the general population. (b) (4) Thus, the low dose group doesn't have an advantage over sham in the overall population when considering both this risk and this benefit.

(b) (4)

Table 6: Risk - Benefit assessment in the overall population, integrated FAME studies observed cases

Risk	Risk/benefit categories	Definition of risk and benefit	Sham	Low dose
cataract surgery	Benefit and no harm	Benefit = BCVA Improvement from baseline of 15 letters or more at anytime No harm = no cataract surgery	24/113 (21%)	13/235 (5%)
	no benefit and harm	No Benefit = No BCVA improvement from baseline of 15 letters or more at Month 24 harm = cataract surgery	16/113 (14%)	78/235 (33%)
Increase IOP	Benefit and no harm	Benefit = BCVA improvement from baseline of 15 letters or more at any time No harm= no IOP increase and no ocular hypertension	57/185 (31%)	115/375 (31%)
	No benefit and harm	No benefit = No BCVA improvement from baseline of 15 letters or more at any time Harm = IOP increase or ocular hypertension	19/185 (10%)	69/375 (18%)

Reference: Applicant's Table 59 and Table 61 in the Efficacy Information Amendment of the current submission (see Appendix).

Table 7: Risk-benefit assessment in the overall population, DME (b) (4) **subgroup**

(b) (4)

Reference: Applicant's Table ISE.48 and Table 62 in the Efficacy Information Amendment of the current submission (see Appendix)

7 Recommendations

In summary, the main review issue with the results of this submission is the same as with the original NDA, that is weighing the benefit of Iluvien treatment on improving Best Corrected Visual Acuity (BCVA) against its risks of causing elevated Intra Ocular Pressure (IOP) and cataract formation and surgery.

We defer to the clinical review to weigh the benefit against the risk of this drug in the general population or in the subgroup of DME (b) (4) but the drug harms a significantly higher proportion of subjects compared to sham. The two main harms considered here are IOP elevation or cataract surgery. (b) (4) The statistical review cannot weigh the benefit of BCVA gain versus the risk of cataract surgery or elevated IOP and we defer for the clinical review team to weigh these outcomes against each other.

8 APPENDIX

Table 8: BCVA Change from Baseline Over Time, Full Analysis Population

		Mean BCVA change from baseline			
Study	Visit	Sham	Low Dose	Difference	95% CI for difference
Fame A	(b) (4)				
	Month 24	3.2	3.7	0.4	(-3.8 , 4.6)
	(b) (4)				
Fame B					
	Month 24	0	5.1	5.1	(0.7 , 9.4)
	(b) (4)				

Figure 9: Cumulative Distribution Function of BCVA Change from Baseline in Sham and Low Dose at Month 30 in FAME B, Full Analysis Population

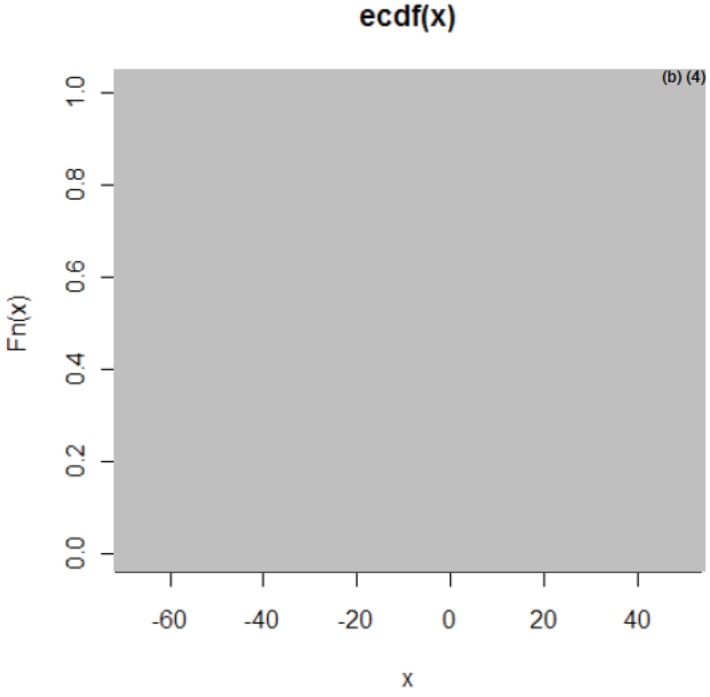

Figure 10 : Cumulative Distribution Function of BCVA Change from Baseline in Sham and Low Dose at Month 36 in FAME B, Full Analysis Population

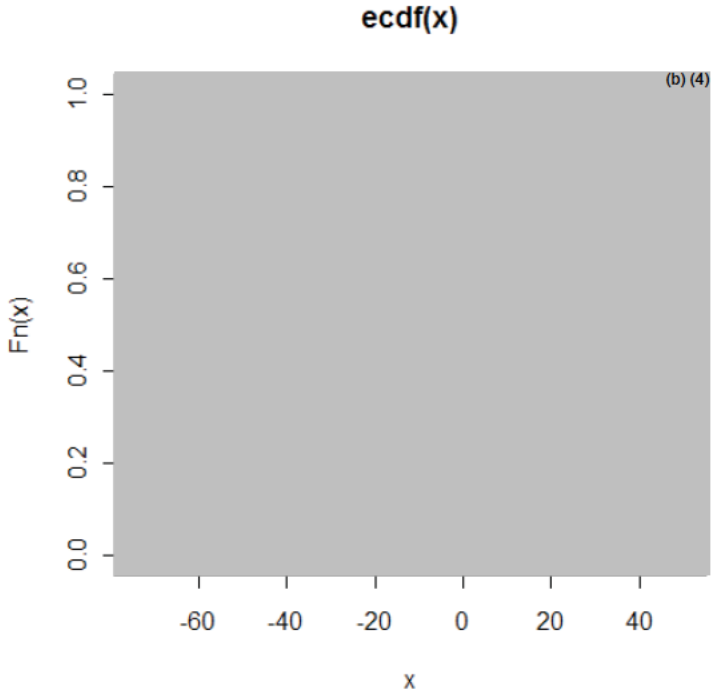

Table 9: Proportion of Subjects with BCVA Increase from Baseline of 15 or More In Different Subgroups in FAME A and FAME B at Month 24, Full Analysis Population

	FAME A			FAME B		
	Sham n/N (%)	Low Dose n/N (%)	Difference and 95% CI	Sham n/N (%)	Low Dose n/N (%)	Difference and 95% CI
Overall , study	14 / 95 (15 %)	51 / 190 (27 %)	12.1 (1.8 , 22.4)	16 / 90 (18 %)	57 / 186 (31 %)	12.9 (1.7 , 24.0)
Age , < median	7 / 50 (14 %)	31 / 86 (36 %)	22.0 (6.5 , 37.6)	9 / 48 (19 %)	32 / 93 (34 %)	15.7 (-0.6 , 31.9)
Age , >= median	7 / 45 (16 %)	20 / 104 (19 %)	3.7 (-10.9 , 18.3)	7 / 42 (17 %)	25 / 93 (27 %)	10.2 (-5.9 , 26.4)
Race , White	12 / 70 (17 %)	40 / 139 (29 %)	11.6 (-1.0 , 24.3)	11 / 62 (18 %)	37 / 126 (29 %)	11.6 (-2.0 , 25.2)
Race , Other	2 / 25 (8 %)	11 / 51 (22 %)	13.6 (-4.9 , 32.1)	5 / 28 (18 %)	20 / 60 (33 %)	15.5 (-5.7 , 36.6)
Sex , Male	7 / 47 (15 %)	26 / 80 (32 %)	17.6 (1.5 , 33.7)	4 / 30 (13 %)	22 / 81 (27 %)	13.8 (-4.0 , 31.7)
Sex , Female	7 / 48 (15 %)	25 / 110 (23 %)	8.1 (-6.0 , 22.3)	12 / 60 (20 %)	35 / 105 (33 %)	13.3 (-1.5 , 28.2)
Iris Color , Dark	9 / 49 (18 %)	24 / 93 (26 %)	7.4 (-8.1 , 23.0)	11 / 58 (19 %)	37 / 127 (29 %)	10.2 (-3.9 , 24.2)
Iris Color , Light	5 / 45 (11 %)	26 / 95 (27 %)	16.3 (1.8 , 30.7)	5 / 32 16 %)	20 / 59 (34 %)	18.3 (-1.6 , 38.1)
Lens status , Phakic	11 / 61 (18 %)	37 / 124 (30 %)	11.8 (-2.0 , 25.6)	11 / 60 (18 %)	32 / 112 (29 %)	10.2 (-3.9 , 24.4)
Lens status , Pseudophakic	3 / 34 (9 %)	14 / 66 (21 %)	12.4 (-3.6 , 28.3)	5 / 30 (17 %)	25 / 74 (34 %)	17.1 (-2.4 , 36.6)
Baseline HbA1c , < median	6 / 37 (16 %)	37 / 124 (30 %)	13.6 (-2.5 , 29.7)	9 / 42 (21 %)	24 / 70 (34 %)	12.9 (-5.7 , 31.4)
Baseline HbA1c , >= median	6 / 44 (14 %)	14 / 66 (21 %)	7.6 (-8.5 , 23.6)	4 / 34 (12 %)	25 / 92 (27 %)	15.4 (-0.7 , 31.6)
Area of fluorescein leakage , < median	8 / 46 (17 %)	31 / 100 (31 %)	13.6 (-2.2 , 29.4)	8 / 41 (20 %)	21 / 92 (23 %)	3.3 (-13.3 , 19.9)
Area of fluorescein leakage , >= median	5 / 47 (11 %)	19 / 83 (23 %)	12.3 (-2.0 , 26.5)	8 / 44 (18 %)	35 / 90 (39 %)	20.7 (3.8 , 37.6)
Area of cystoid changes , < median	10 / 45 (22 %)	24 / 88 (27 %)	5.1 (-11.9 , 22.0)	11 / 49 (22 %)	24 / 83 (29 %)	6.5 (-10.4 , 23.3)
Area of cystoid changes , >= median	3 / 48 (6 %)	26 / 95 (27 %)	21.1 (8.3 , 34.0)	5 / 36 (14 %)	32 / 99 (32 %)	18.4 (2.0 , 34.9)
Capillary loss , < median	9 / 48 (19 %)	37 / 116 (32 %)	13.1 (-2.2 , 28.5)	9 / 46 (20 %)	32 / 102 (31 %)	11.8 (-4.3 , 28.0)
Capillary loss , >= median	4 / 36 (11 %)	9 / 51 (18 %)	6.5 (-10.5 , 23.6	6 / 29 (21 %)	16 / 54 (30 %	8.9 (-12.8 , 30.7)

	FAME A			FAME B		
	Sham n/N (%)	Low Dose n/N (%)	Difference and 95% CI	Sham n/N (%)	Low Dose n/N (%)	Difference and 95% CI
			)		)	
Continent , European Union	1 / 9 (11 %)	2 / 16 (12 %)	1.4 (-26.2 , 28.9)	1 / 8 (12 %)	5 / 21 (24 %)	11.3 (-26.6 , 49.2)
Continent , Asian subcontinent	1 / 19 (5 %)	6 / 39 (15 %)	10.1 (-8.9 , 29.2)	4 / 20 (20 %)	14 / 41 (34 %)	14.1 (-12.3 , 40.6)
Continent , North America	12 / 67 (18 %)	43 / 135 (32 %)	13.9 (0.7 , 27.1)	11 / 62 (18 %)	38 / 124 (31 %)	12.9 (-0.8 , 26.6)
Duration of diabetes , < median	9 / 52 (17 %)	30 / 117 (26 %)	8.3 (-6.0 , 22.7)	8 / 58 (14 %)	34 / 125 (27 %)	13.4 (0.3 , 26.5)
Duration of diabetes , >= median	5 / 42 (12 %)	21 / 72 (29 %)	17.3 (1.0 , 33.5)	8 / 32 (25 %)	23 / 61 (38 %)	12.7 (-9.0 , 34.4)
Type of diabetes , type 1	0 / 8 (0 %)	6 / 16 (38 %)	37.5 (4.4 , 70.6)	0 / 5 (0 %)	6 / 13 (46 %)	46.2 (5.2 , 87.1)
Type of diabetes , type 2	13 / 86 (15 %)	45 / 170 (26 %)	11.4 (0.4 , 22.3)	16 / 84 (19 %)	51 / 171 (30 %)	10.8 (-1.0 , 22.5)
Steroid injections , yes	1 / 19 (5 %)	10 / 38 (26 %)	21.1 (-0.1 , 42.2)	2 / 17 (12 %)	12 / 34 (35 %)	23.5 (-3.1 , 50.1)
Steroid injections , no	13 / 75 (17 %)	40 / 148 (27 %)	9.7 (-2.5 , 21.9)	13 / 71 (18 %)	44 / 146 (30 %)	11.8 (-0.9 , 24.5)
Baseline BCVA , <49 letters	6 / 26 (23 %)	29 / 60 (48 %)	25.3 (2.0 , 48.6)	8 / 23 (35 %)	24 / 55 (44 %)	8.9 (-17.7 , 35.4)
Baseline BCVA , >=49 letters	8 / 69 (12 %)	22 / 130 (17 %)	5.3 (-5.7 , 16.4)	8 / 67 (12 %)	33 / 131 (25 %)	13.3 (1.4 , 25.1)
Duration of DME (b) (4)	[redacted]					(b) (4)
Duration of DME (b) (4)						

Table 10: BCVA Change from Baseline in Different Subgroups in FAME A and FAME B at Month 24, Full Analysis Population

	FAME A				FAME B			
	Sham	Low Dose	Difference (Low Dose – Sham)	95% CI	Sham	Low Dose	Difference (Low Dose – Sham)	95% CI
Overall , this study	2.9	4.8	1.9	(-2.5 , 6.2)	-0.3	6.7	7	(2.6 , 11.3)
Age , < median	3.3	6	2.7	(-4.1 , 9.6)	0.2	8.1	7.8	(2.2 , 13.5)
Age , >= median	2.5	3.8	1.2	(-4.4 , 6.9)	-0.9	5.3	6.2	(-0.6 , 12.9)
Race , white	2.2	6.2	4	(-1.0 , 8.9)	-1.4	5.8	7.2	(1.6 , 12.9)
Race , Other	4.9	0.9	-4	(-13.4 , 5.5)	2.2	8.5	6.2	(-0.3 , 12.7)
Sex , Male	3.8	4.4	0.7	(-5.2 , 6.5)	0.1	7.4	7.3	(1.6 , 12.9)
Sex , Female	2	5.2	3.2	(-3.6 , 10.0)	-1.1	5.7	6.9	(-0.1 , 13.9)
Continent , Europe	3.1	7.5	4.5	(-0.5 , 9.4)	-0.9	7.4	8.3	(2.8 , 13.7)
Continent , Asia	1	-1.3	-2.3	(-16.2 , 11.5)	-2.9	-0.9	2	(-12.3 , 16.3)
Continent , North America	3.2	-2.4	-5.5	(-16.8 , 5.7)	2.6	8.5	5.8	(-2.7 , 14.4)
Iris Color , Dark	4.6	4.2	-0.3	(-6.4 , 5.8)	1.2	6.1	5	(-0.2 , 10.2)
Iris Color , Light	1	5.1	4.1	(-2.4 , 10.6)	-2.9	7.9	10.7	(2.7 , 18.8)
BCVA , < 49 letters	7.7	15	7.3	(-0.5 , 15.0)	1.9	12	10.1	(0.9 , 19.4)
BCVA , >=49 letters	1.1	0	-1.1	(-6.0 , 3.9)	-1	4.4	5.5	(0.6 , 10.3)
lens status , Pseudophakic	0.9	5.5	4.6	(-2.4 , 11.5)	-2.3	7.8	10.1	(2.2 , 17.9)
lens status , Phakic	4	4.4	0.4	(-5.3 , 6.1)	0.7	6	5.2	(-0.0 , 10.5)
Baseline HbA1c , < median	4.1	7.3	3.2	(-2.7 , 9.0)	0.9	6.8	5.9	(-1.3 , 13.1)
Baseline HbA1c , >= median	0.9	4.3	3.5	(-3.1 , 10.0)	-3.5	6.4	9.8	(3.1 , 16.5)
Steroid injection , No	3.2	5.3	2.1	(-2.9 , 7.1)	-0.3	6.7	7	(1.9 , 12.1)
Steroid injection , Yes	1.9	4.2	2.3	(-7.4 , 11.9)	0.8	7.1	6.3	(-2.5 , 15.1)
Area of fluorescein leakage , < median	6.3	6.3	0	(-6.3 , 6.3)	2.9	3.6	0.8	(-5.1 , 6.7)
Area of fluorescein leakage , >= median	-0.7	3.2	4	(-2.0 , 9.9)	-3	9.5	12.5	(5.8 , 19.2)
Area of cystoid change , < median	5.1	3.8	-1.3	(-7.7 , 5.0)	-0.6	7.3	7.9	(2.1 , 13.7)
Area of cystoid change , >= median	0.5	6	5.5	(-0.6 , 11.6)	0.4	5.9	5.5	(-1.6 , 12.6)
Capillary Loss , < median	6	6.2	0.2	(-5.7 , 6.1)	-1.4	7.3	8.7	(2.9 , 14.5)
Capillary Loss , >= median	-0.4	0	0.4	(-6.9 , 7.7)	0.1	6.5	6.4	(-1.3 , 14.1)
Duration of Diabetes , < median	1.6	1.9	0.3	(-6.7 , 7.3)	0.6	7.6	7.1	(0.2 , 13.9)
Duration of Diabetes , >= median	4	7.2	3.2	(-2.4 , 8.7)	-0.9	6	6.9	(1.1 , 12.6)
Type of Diabetes , Type 1	-5.1	12.8	17.9	(3.6 , 32.2)	-4.2	13.7	17.9	(4.4 , 31.4)
Type of Diabetes , Type 2	3.5	4.1	0.6	(-4.0 , 5.3)	0	6.2	6.2	(1.6 , 10.8)
Duration of DME , (b) (4)	(b) (4)							
Duration of DME , (b) (4)								

Table 11: Analysis of Association Between ≥15 Letter BCVA Improvement at Any Time and Cataract Operation (Observed Cases)

Source: Table 59 in the Efficacy Information Amendment of the current submission

	Any Report of Cataract Operation				(b) (4)
≥15 letter Improvement AT ANY TIME	**Sham n (%)**		**0.2 µg/day FA n (%)**		
	YES	**NO**	**YES**	**NO**	
YES	17 (51.5)	24 (27.3)	110 (58.5)	13 (27.7)	
NO	16 (48.5)	64 (72.7)	78 (41.5)	34 (72.3)	
Total	33 (100)	88 (100)	188 (100)	47 (100)	
P-value (Pearson's chi-square)	0.012		<0.001		
P-value (Homogeneity vs. Sham)			0.633		
P-value (Homogeneity Actives)					

Table 12: Association Between Increased IOP/Ocular Hypertension and Improvement in BCVA (Integrated FAME Studies, Observed Cases)

Source: Table 61 in the Efficacy Information Amendment of the current submission

	Any Report of Increased IOP or Ocular Hypertension				(b) (4)
≥15 letter Improvement	**Sham n (%)**		**0.2 µg/day FA n (%)**		
	YES	**NO**	**YES**	**NO**	
YES	3 (13.6)	57 (35.0)	70 (50.4)	115 (48.7)	
NO	19 (86.4)	106 (65.0)	69 (49.6)	121 (51.3)	
Total	22 (100)	163 (100)	139 (100)	236 (100)	
P-value (Pearson's chi-square)	0.045		0.760		
P-value (Homogeneity vs. Sham)			0.047		
P-value (Homogeneity Actives)					

Table 13: Association Between Increased IOP/Ocular Hypertension and Improvement in BCVA (Integrated Duration of DME (b) (4) Subgroup, Observed Cases)

Source: Table 62 in the Efficacy Information Amendment of the current submission

(b) (4)

Table 14: Association Between Cataract Surgery and Improvement in Best Corrected Visual Acuity (Population: Safety)

Source: Table ISE.48 in the Efficacy Information Amendment of the current submission

	Any Report of Cataract Operation Through Visit					
	Sham		0.2 ug/day		0.5 ug/day	
15-Letter Improvement By Visit	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Month 6						(b) (4)
Yes	0 (0.0%)	0 (0.0%)	4 (100%)	28 (26.7%)		
No	3 (100%)	63 (100%)	0 (0.0%)	77 (73.3%)		
Total	3 (100%)	63 (100%)	4 (100%)	105 (100%)		
P-value (Chi-sq)		0.056		0.002		
P-value (Homogeneity vs. Sham)				N/A		
P-value (Homogeneity Actives)						
Month 12						
Yes	2 (25.0%)	3 (5.5%)	9 (60.0%)	13 (14.6%)		
No	6 (75.0%)	52 (94.5%)	6 (40.0%)	76 (85.4%)		
Total	8 (100%)	55 (100%)	15 (100%)	89 (100%)		
P-value (Chi-sq)		0.016		<0.001		
P-value (Homogeneity vs. Sham)				0.722		
P-value (Homogeneity Actives)						
Month 24						
Yes	6 (40.0%)	4 (10.8%)	35 (53.0%)	3 (13.0%)		
No	9 (60.0%)	33 (89.2%)	31 (47.0%)	20 (87.0%)		
Total	15 (100%)	37 (100%)	66 (100%)	23 (100%)		
P-value (Chi-sq)		0.795		<0.001		
P-value (Homogeneity vs. Sham)				0.751		
P-value (Homogeneity Actives)						
Month 30						
Yes	2 (12.5%)	3 (10.0%)	39 (50.0%)	2 (22.2%)		
No	14 (87.5%)	27 (90.0%)	39 (50.0%)	7 (77.8%)		
Total	16 (100%)	30 (100%)	78 (100%)	9 (100%)		
P-value (Chi-sq)		0.126		0.114		
P-value (Homogeneity vs. Sham)				0.428		
P-value (Homogeneity Actives)						
Month 36						
Yes	4 (22.2%)	2 (6.9%)	35 (43.2%)	0 (0.0%)		
No	14 (77.8%)	27 (93.1%)	46 (56.8%)	3 (100%)		
Total	18 (100%)	29 (100%)	81 (100%)	3 (100%)		
P-value (Chi-sq)		N/A		0.136		
P-value (Homogeneity vs. Sham)				0.437		
P-value (Homogeneity Actives)						

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/s/

RIMA IZEM
07/29/2011

YAN WANG
08/01/2011
I concur with the primary statistical review.

NDA 201923
Document number: 22
Drug: FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT 0.19 mg
Indication: Diabetic Macular edema
Applicant: Alimera Sciences Inc
Meeting Package Received: 01/21/2011
Meeting Date: 02/02/2011
Statistical Reviewer: Rima Izem
Statistical team leader: Yan Wang

Statistical comments on Sensitivity Analyses

Please consider the following comments and resubmit your statistical analysis plan for review. Our comments regarding sensitivity analyses 2 and 3 are separated into three parts, corresponding to the three steps in multiple imputations:

1- Comments on proposed imputation step which generates m complete datasets
2- Comments on proposed analysis step which fits an analysis model to each of the m complete data sets
3- Comments on proposed combination step which combines the estimates from all complete data sets' fits

We also provide comments on data to submit regarding the sensitivity analyses as well as documentation to provide with the results.

Comments on proposed imputation step generating m complete datasets:

1- We agree with the following:
    a- Total number of complete dataset m to be 25. This is a reasonable number of complete datasets to be generated from multiple imputations method considering the amount of missing values at month 24. If the percent of missing values exceeds 30% at month 36, you should consider increasing m accordingly.
    b- Strategy of imputing the continuous BCVA first and deriving the binary primary variable from that BCVA imputations and the baseline BCVA.

2- We recommend that you consider the following changes to your proposal:

    a- Use a different procedure than PROC MI for the imputation step. PROC MI assumes multivariate normality of the data. Since in our next comment we propose that you consider a larger model with both continuous and categorical variables, the assumption of multivariate normality is unlikely to hold. The paper by Horton and Kleinman (2007) provides a good

review of statistical methods and statistical packages handling the mix of continuous and categorical variables (for example using the chained equations method with IVEware in SAS or MICE library in R and Splus). The more recent MI library in R also handles this type of models.

b- Include additional variables in the imputation model. Multiple imputations methods assume that the data is missing at random (MAR), so it is important that the imputation model includes any variable which may either be associated to BCVA or to missingness. For instance, in addition to BCVA over time, the model could include all baseline characteristics[1] and cataract timing information. Experts in MI methods recommend that the imputation models include variables to be used in the analysis step, so including the treatment assignment in the imputation models is recommended. Interaction terms between these variables may be included if they improve the models' fit. Transformation of some variables (such as box-cox) may be necessary to insure convergence of fitting algorithms.

c- Do not replace BCVA measurements of subjects who dropped out (resp. who died) by their baseline BCVA before the imputation step in sensitivity analysis 2 (resp. sensitivity analysis 3). Instead, impute all missing BCVA first in the imputation step. Then, derive the binary primary outcome and replace the binary outcome for all dropouts (resp. deaths) by failure before the analysis step in sensitivity analysis 2 (resp. sensitivity analysis 3).

d- There is no need to round off the BCVA continuous measurement from the imputation step.

Comments on proposed analysis step:
In the analysis step, tests and confidence intervals are derived for the binary primary endpoint based on each complete dataset. In Subsection 7.3, you propose (b) (4)

However, in Subsection 7.4, you propose (b) (4)

Since the derived p-value in your primary analysis adjusts for stratification (CMH method), we recommend that your confidence intervals in the analysis step (for all

[1] Baseline characteristics to consider are: baseline BCVA, gender, age, race, iris color, diabetes history, diabetes treatment, baseline HbA1c, study eye, time since diagnosed with DME, study eye lens status at baseline, steroid injection in study eye, intravitreal anti-VEGF treatment, baseline intraocular pressure, and presence of cataract at baseline.

sensitivity analyses) also correct for stratification. To correct for stratification using the same assumptions as CMH, you can use the method proposed by Mehrotra and Railkar (2000).

Comments on combination step:
Note that in your formulas in Subsection 7.4, [redacted] (b) (4)

In the combined 95% confidence interval, we would prefer that you use the t statistic with degrees of freedom v instead of the proposed [redacted] (b) (4)
where v is given by the formula:

$$v = (m - 1)\ (1 + U/(\ (1 + m^{-1})B\ )^2$$

What to submit to FDA regarding the sensitivity analyses:

Please submit the following:

- The derived variable for sensitivity analysis 1
- All complete imputed datasets for sensitivity analysis 2 and sensitivity analysis 3
- Code performing the imputation for sensitivity analysis 2 and sensitivity analysis 3

What to describe in the results section of sensitivity analyses:

We recommend that you provide the following (see Box 3 of Sterne et al 2009):

- Report the number of missing values for each variable of interest, or the number of cases with complete data for each important component of the analysis. Give reasons for missing values if possible.
- For analyses based on multiple imputation:
    - Provide details of the imputation modeling: Report details of the software used and of key settings for the imputation modeling. Report the number of imputed datasets that were created.
    - What variables were included in the imputation procedure? How were non-normally distributed and binary/categorical variables dealt with
    - If a large fraction of the data is imputed, compare observed and imputed values. Where possible, provide results from analyses restricted to complete cases, for comparison with results based on multiple imputation. If there are important differences between the results, suggest explanations, bearing in mind that analyses of complete cases may suffer more chance variation, and that under the missing at random assumption

multiple imputation should correct biases that may arise in complete cases analyses
    - Discuss whether the variables included in the imputation model make the missing at random assumption plausible

- Exploratory figures (1) checking for convergence of MCMC algorithm or Gibbs sampler (2) comparing imputed values to observed values.

References:

Horton, Nicholas J. and Ken P. Kleinman. (2007) Much Ado About Nothing: A Comparion of Missing Data Methods and Software to Fit Incomplete Data Regression Models. The American Statistician 61(1, February):79–90.

Mehrotra DV, Railkar R. (2000) Minimum risk weights for comparing treatments in stratified binomial trials. Statistics in Medicine 2000; 19:811– 825.

Sterne JA, White IR, Carlin JB, et al Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338. b2393. (doi: 10.1136/bmj.b2393).

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/s/

RIMA IZEM
03/07/2011

YAN WANG
03/07/2011

Addendum to Statistical Review

NDA/Serial Number:	201923 / N000
Drug Name:	Lluvien, **Fluocinolone Acetonide Intravitreal Insert 0.19mg**
Indication(s):	Diabetic Macular Edema
Applicant:	**Alimera Sciences Inc.**
Date(s):	Submitted date: June 28th, 2010 Received date: June 30th, 2010 PDUFA goal date: December 30th, 2010
Review Priority:	Priority
Biometrics Division:	DB 4
Statistical Reviewer:	Rima Izem
Concurring Reviewers:	Yan Wang
Medical Division:	DAIOP
Clinical Team:	Clinical Reviewer: Martin Nevitt. Clinical Team Leader: William Boyd.
Project Manager:	Dean Jane

Keywords: Diabetic Macular Edema, Risk-Benefit analysis, Cataract Adverse Event

This addendum to the statistical review corrects a typographical error of the NDA/Serial Number listed on page 1 of the Statistical Review submitted on 11/30/2010 in DARRTS. The NDA/Serial Number for this application was incorrectly listed as 209123/N00 in the Statistical Review. The correct NDA/Serial Number is 201923/N000.

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/s/

RIMA IZEM
12/10/2010

YAN WANG
12/10/2010
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 201923 **Applicant: Alimera Sciences Inc.** **Stamp Date: 06/30/2010**

Drug Name: Iluvien Fluocinolone Acetonide Intravitreal Insert 0.19mg **NDA/BLA Type: Priority review**

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			Tables for efficacy for Sex and Race are not available in the summary of clinical efficacy. However, subgroups in these variables are discussed in each study report
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Request was made to clarify the define.pdf file for adverse events as well as provide additional analysis datasets

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____Yes___

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

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Efficacy was investigated in several populations. However, simple investigation of baseline characteristics of dropouts has not been conducted.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials
The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
FAME A: C-01-05-001a	Mutlicenter, randomized, double masked, sham controlled study in subjects with DME who had undergone previous laser therapy.	(1) sham injection (95 subjects), (2) 0.2 µg/day FA intravitreal insert (190 subjects), or (3) 0.5 µg/day FA intravitreal insert (196 subjects).	Proportion of subjects with a larger or equal to 15 letter increase from baseline in best corrected visual acuity (BCVA) in the study eye at Month 24.	Showed a significant effect of both doses on Effective Population.
FAME B: C-01-05-001b	Multicenter, randomized, double masked, sham controlled study inserts in subjects with DME who had undergone previous laser therapy.	(1)sham injection (90 subjects), (2) 0.2 µg/day FA intravitreal insert (186 subjects), or (3) 0.5 µg/day FA intravitreal insert (199 subjects).	Proportion of subjects with a larger or equal to 15 letter increase from baseline in best corrected visual acuity (BCVA) in the study eye at Month 24.	Showed a significant effect of both doses on Effective Population.

Regulatory background:

Fluocinolone Acetonide, the drug substance in Iluvien, is a corticosteroid. It is also the active agent in Retisert® (Bausch & Lomb, Rochester, NY), an intraocular delivery implant approved in 2005 by the Food and Drug Administration (FDA) (but not elsewhere) for treatment of non-infectious posterior uveitis.

Current proven treatments for DME include laser therapy and tight diabetic control. There is currently no approved drug for this indication.

Summary of main issues:

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Risk/benefit:
Although both studies made their primary efficacy endpoints (Change from baseline of BCVA at 2 years greater or equal to 15 letters), there are safety concerns about this drug
1- A very significant increase of cataract and cataract surgery in the treatment groups compared to the Sham in both studies
2- A higher proportion of subjects with decreased vision (at least 15 letters decrease in BCVA) in the treatment group compared to the sham group.
3- A higher proportion of subjects with SAE in the treatment groups compared to the sham group.

Issue with primary endpoints/primary analysis:

- Some of these treatment induced safety concerns (cataract/ cataract surgery) as well as other concomitant treatments (laser treatment or anti-VEGF medication) may be confounding the primary efficacy parameter of the drug at 24 months. Effect of these confounding variables will be investigated.
- About 20% of the data for the primary efficacy endpoint is missing. Effect of the missing values on the primary analyses will be investigated

Other issues:

- Although the two trials had identical protocols, similar recruited population at baseline and similar number and locations of centers, the efficacy results in the three treatment arms were different. Differences between the two studies will be investigated.

Rima Izem	07-28-2010
Reviewing Statistician	Date
Yan Wang	07-28-2010
Supervisor/Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201923	ORIG-1	ALIMERA SCIENCES INC	FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT 0.19 mg

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/s/

RIMA IZEM
08/17/2010

YAN WANG
08/17/2010