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
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STATISTICAL TEAM LEADER REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA203168
Drug Name:	Bromfenac 0.07% Ophthalmic Solution
Indication(s):	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Applicant:	Bausch+Lomb
Date(s):	Stamp date: June 6, 2012 PDUFA date: April 7, 2013
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Biometrics Division:	DBIV
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Keywords: anterior chamber cells, anterior chamber flare, ocular inflammation, ocular pain, cataract surgery.

Table of Contents

LIST OF TABLES

1 Introduction/Purpose of Review

To provide support for the primary statistical reviewer's recommendation for the labeling, this statistical team leader's review evaluates the analysis of the primary efficacy endpoint of cleared ocular inflammation in the current NDA203168 and compares the analysis to seven previously approved NDAs for the indication of ocular inflammation after cataract surgery.

Specifically, the focus of this review is on the examination of the definition of postoperative ocular inflammation, including its two components of "anterior chamber cell counts and grade scores" and "anterior chamber flare scores", along with the way these individual components were defined and measured, and the determination on the clearance/resolution of ocular inflammation. In addition to the grade and evaluation of ocular inflammation, this review also examines how many time points were included in each application and which time points were considered important in the assessment of efficacy on ocular inflammation. Furthermore for each application, this review also examines whether there were subjects whose ocular inflammation was cleared by week 1 (days 7-8), but was subsequently not cleared at week 2 (days 14-15) post-surgery, and how these subjects were treated in the analysis of the endpoint "cleared ocular inflammation" at days 14-15.

The endpoint of pain resolution is generally a secondary endpoint in these approved NDAs. Information on this endpoint is included in this review for the sake of completeness; however, the statistical team leader has not specifically examined the scales that were scored to evaluate the presence of pain and the resolution of pain. Therefore, the data on pain resolution are taken directly from the clinical and/or statistical reviews. Because the Clinical Studies sections of labeling are presented in their entirety, this review includes whatever information on pain is included in labeling.

The applicant's and the primary reviewer's analyses for the current NDA203168 are presented in Section 2; the analyses for the 7 approved NDAs are presented in Section 3; and Section 4 concludes with the statistical review team's recommendations for the drug labeling for the current NDA.

2 Current NDA203168 Prolensa (bromfenac ophthalmic solution, 0.07% QD)

In support of the efficacy claim, this NDA included two phase 3 studies in subjects who underwent cataract extraction with posterior chamber intraocular lens implantation. These two studies shared a common protocol and a statistical analysis plan and were conducted in the United States. Both studies were randomized, double-masked, multi-center, parallel, and vehicle (placebo)-controlled studies. The major difference between these two studies was: Study 1 included 20 sites in the east region of the United States and Study 2 included 19 sites in the west region of the United States.

Randomization occurred at the screening visit (1 to 8 days prior to surgery). In each study, 220 patients were randomized to receive either bromfenac 0.07% or vehicle in a 1:1 ratio. Subjects

self-instilled 1 drop of study drug (bromfenac 0.07% or vehicle) into the study (operative) eye once daily, beginning 1 day prior to surgery (Day 0), continued on the day of surgery and through the first 14 days post-surgery. Subjects were evaluated on Days 1, 3, 8, 15, 22 following surgery or 7 days after their last dose of the study drug if subjects prematurely discontinued the study drug. Ocular inflammation and pain were assessed at the screening visit and each post-surgery visit. Pain was evaluated by the pain score from the Ocular Comfort Grading Assessment (OCGA) recorded in the subject diary. Regarding the evaluation of ocular inflammation and the primary efficacy outcome of cleared ocular inflammation, the applicant's statistical analysis plan (dated 04/26/2011) states the following:

> *The primary efficacy outcome of cleared ocular inflammation is defined as the proportion of subjects that achieve a summed ocular inflammation score (SOIS) of grade 0 (0 cells and absence of flare) by Day 15. The SOIS is defined as the sum of the mean anterior chamber cells score and anterior flare score. The anterior chamber cell grade is determined twice per study visit, and is based on a manual count of cells using a slit lamp biomicroscopy. Between the two manual cell counts, the biomicroscopy is to be refocused off and back onto the anterior chamber, as a means of obtaining a more precise average estimate. The anterior chamber cell grade and flare grade are determined as follows:*

Anterior Chamber Cells			**Anterior Chamber Flare**	
Grade	**Manual Cell Count**	**Recorded Cell Grade**	**Grade**	**Flare**
0	0	0	0	Complete absence
0.5	1-5 (trace)	0.5	1	Very slight (barely detectable)
1	6-15	1	2	Moderate (iris and lens clear)
2	16-25	2	3	Marked (iris and lens hazy)
3	26-50	3	4	Intense (fibrin clot)
4	>50	4		

> *The anterior chamber cell score at each study visit is defined as the average of both cell grades obtained. If only one grade was collected for any given visit, the cell score will be set to the single cell grade. An anterior chamber cell score of zero is achieved at any given study visit only if both cell grades are zero, or if only a single cell grade is recorded and was observed to be zero. In order to satisfy the primary endpoint of a SOIS of grade zero by Day 15, an anterior chamber cells score of grade zero and an anterior flare score of grade zero must be observed on any scheduled visit on or prior to the Day 15 visit. Each score will be documented on the CRF; the mean values for SOIS will be calculated at the data management level to maintain accuracy.*

The key secondary efficacy endpoint was the proportion of subjects who were pain free ("None" on the Ocular Comfort Assessment) at Day 1. The primary efficacy analysis was conducted on the ITT population (all randomized subjects). For both the primary and key secondary

endpoints, the Fisher's exact test was used to compare the treatment difference. Missing data were imputed using the Last Observation Carried Forward (LOCF) method. The comparisons of the endpoint of cleared ocular inflammation (0 cell and no flare) at multiple time points (Day 1, 3, and 8) were adjusted for multiplicity using the Hochberg method.

The applicant's primary analysis results are presented in Table 2.1. Compared with vehicle, the bromfenac group had a statistically significantly higher proportion of subjects who had cleared ocular inflammation by Day 15 and a statistically significantly higher proportion of subjects who were pain free at Day 1. Compared with vehicle, after adjusting for multiplicity (due to testing the endpoint of ocular inflammation at 4 time points) using the protocol-defined Hochberg method, the bromfenac group also had a statistically significantly higher proportion of subjects who had cleared ocular inflammation by Day 8.

Table 2. 1 NDA203168: Applicant's Efficacy Analysis Results of Phase 3 Studies

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Bromfenac 0.07% QD	**Vehicle QD**	**Difference (%) (Asymptotic 95% CI)**
Study 1	Day 8	30/112 (26.8%)	8/108 (7.4%)	19.4 (9.8, 28.9)
	Day 15 (primary*)	54/112 (48.2%)	18/108 (16.7%)	31.5 (19.9, 43.2)
Study 2	Day 8	36/110 (32.7%)	18/110 (16.4%)	16.4 (5.2, 27.5)
	Day 15 (primary*)	54/ 110 (49.1%)	35/ 110 (31.8%)	17.3 (4.5, 30.0)
		Proportion of Subject who Were Pain Free (0 pain score)		
Study 1	Day 1	91 (81.3%)	47 (43.5%)	37.7 (25.9, 49.6)
Study 2	Day 1	84 (76.4%)	61 (55.5%)	20.9 (8.7, 33.1)

Data Source: Table 2 of the primary statistical review dated 04/01/2013 (the p-values presented in the table were adjusted p-values using the Hochberg method).
*This is stated as primary endpoint; however, some subjects who did not have a cell score of Grade 0 (0 cell) at Day 15 were treated as successes in this analysis. The FDA statistical reviewer's analysis in Table 2.3 treated these subjects as failures.

As shown in Table 2.2, for the two studies combined, there were 15 subjects in both treatment groups whose ocular inflammation was cleared at or prior to Day 8 but was not cleared at Day 15. Among them, 13 (87%) subjects had a cell score of Grade 0.5 (1-5 cells), and 2 (13%) subjects had a cell score of Grade 1 (6-15 cells). These 15 subjects were counted as successes in the applicant's analysis in Table 2.1, although these subjects had a cell count in the range of 1-15 cells at Day 15 and a cell count of 0 at baseline (screening visit).

These 15 subjects were treated as failures in the FDA's statistical reviewer's analysis presented in Table 2.3. Compared with the applicant's analysis, the statistical reviewer's analysis yielded a lower success rate at Day 15 for both treatment groups: 45.5% vs. 48.2% in the bromfenac

group, and 13.0% vs. 16.7% in the vehicle group in Study 1; 45.4% vs. 49.1% in the bromfenac group, and 27.3% vs. 31.8% in the vehicle group in Study 2. The treatment differences in the FDA's analysis were similar to the applicant's analysis at both visit time points.

The numbers of subjects who received a rescue therapy were: 40 (4 in the bromfenac group and 36 in the vehicle group) in Study 1 and 41 (8 in the bromfenac group and 33 in the vehicle group) in Study 2. It should be noted that the applicant's LOCF analysis has imputed failures for all subjects who received a rescue therapy except for 1 vehicle-treated subject in Study 2. This subject was treated as failure in the FDA's analysis in Table 2.3.

(b) (4)

in the following section this review examines the analysis results for the NDAs that were submitted and approved since 2004 for the treatment of ocular inflammation after cataract surgery.

Table 2. 2 NDA203168: Number of Subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8, but was not cleared (cell score or flare score >0) at Day 15

Study	# of subjects	Cell Score at Day 15					
		Grade 0 (0 cell)	Grade 0.5 (1-5 cells)	Grade 1 (6-15 cells)	Grade 2 (16-25 cells)	Grade 3 (26-50 cells)	Grade 4 (>50 cells)
Study 1							
Bromfenac	3	0	3	0	0	0	0
Vehicle	4	0	4	0	0	0	0
Total	7	0	7	0	0	0	0
Study 2							
Bromfenac	4	0	4*	0	0	0	0
Vehicle	4	0	2	2**	0	0	0
Total	8	0	6	2	0	0	0
Pooled							
Bromfenac	7	0	7	0	0	0	0
Vehicle	8	0	6	2	0	0	0
Total	15	0	13	2	0	0	0
		Flare Score at Day 15					
		Grade 0		Grade 1	Grade 2	Grade 3	Grade 4
Study 1							
Bromfenac	3	2		1	0	0	0
Vehicle	4	1		3	0	0	0
Total	7	3		4	0	0	0
Study 2							
Bromfenac	4	3		1	0	0	0
Vehicle	4	3		1	0	0	0
Total	8	6		2	0	0	0

Data Source: Calculated by the statistical review team.
*Two subjects had "0" cell score for the first grade and "0.5" cell score for the second grade and two subjects had "0.5" cell score for both grades. ** One subject had a cell score of "1" for both grades and one subject had "1" cell score for the first grade and "0" cell score for the second grade.

Table 2. 3 NDA203168: FDA's Primary Statistical Reviewer's Analysis Results of Phase 3 Studies

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Bromfenac 0.07% QD	Vehicle QD	Difference (%) (Asymptotic 95% CI)
Study 1	Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6 (8.4, 26.8)
	Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5 (21.4, 43.8)
Study 2	Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3 (6.7, 27.9)
	Day 15	50/ 110 (45.4%)	30*/ 110 (27.3%)	18.2 (5.7, 30.7)

Data Source: Table 1 from the primary statistical review dated 04/01/2013. Note: The adjusted p-values using the Hochberg method were < 0.05 for the treatment difference at both time points (Day 8 and Day 15).
* One subject who received a rescue therapy was treated as failure in the FDA' analysis and this subject was treated as success in the applicant's analysis in Table 2.1.

3 Efficay Analysis Evaluations of 7 Approved NDAs for the Treatment of Ocular Inflammation after Cataract Surgery

A total of 7 NDAs (see Table 3.0) were submitted and approved for the treatment of ocular inflammation after cataract surgery since 2004. For each of these 7 NDAs, this review presents, in Section 3.1 through 3.7, the findings on how ocular inflammation was defined and analyzed and what information was included in the Clinical Studies section of the labeling. For each of these 7 NDAs, this review also examines whether there were subjects whose ocular inflammation was cleared by week 1 (days 7-8) but was not cleared at week 2 (days 14-15) post-surgery, and how these subjects were treated in the analysis for the endpoint of cleared ocular inflammation, as this is the difference in the applicant's and the statistical reviewer's analyses for the current NDA203168.

Table 3.0: List of NDAs Approved in 2005-2012 for post-operative Inflammation after Cataract Surgery

NDA	Submitted	Approved
3.1 NDA021664 Xibrom (bromfenac ophthalmic solution, 0.09% BID)	2004	2005
3.2 NDA021862 Nevanac (nepafenac ophthalmic suspension, 0.1% TID)	2005	2005
3.3 NDA022212 Durezol (difluprednate ophthalmic emulsion, 0.05%)	2007	2008
3.4 NDA021664 Bromday (bromfenac ophthalmic solution, 0.09% QD)	2009	2010
2.5 NDA200738 Lotemax (loteprednol etabonate ophthalmic ointment, 0.5% QID)	2009	2010
3.6 NDA202872 Lotemax (loteprednol etabonate ophthalmic gel, 0.5% QID)	2011	2012
3.7 NDA203491 Ilevro (nepafenac ophthalmic suspension, 0.3% QD)	2011	2012

It is noted that the title for Section 3.1 through 3.7 contains the exact wordings of indication from the labeling of each approved drug.

3.1 NDA021664 Xibrom (bromfenac ophthalmic solution, 0.09% BID) for the treatment of postoperative inflammation in patients who have undergone cataract extraction

This NDA submission was a paper submission and only the datasets (with blank CRF) were submitted electronically. Thus, the statistical team leader does not have access to the study reports/protocols/analysis plans from this submission. The study designs/analysis plans discussed below are from the primary medical review by Dr. Jennifer Harris dated 03/14/2005.

This NDA included two identically-designed, randomized, and double-masked phase 3 studies in subjects who underwent cataract extraction with posterior chamber intraocular lens implantation. One day after surgery, subjects were randomized to receive the test product or vehicle in a 2:1 ratio. Subjects self-instilled study drug (test product or vehicle) into the study (operative) eye twice a day for 14 days, beginning 1 day after surgery. Anterior chamber cell score and flare score were used to assessed ocular inflammation at the screening visit (1 to 7 days prior to surgery) and each post-surgery visit: Day 1, 3, 8, 15, 22, and 29 or early exit visit.

Regarding the definition of the original primary endpoint, the primary medical review (on page 13) reported the following:

> *The original primary efficacy endpoint for the phase 3 trials proposed by the sponsor was defined as a summed ocular inflammation score (i.e. cell+ flare) ≤ 1 within the 14-day treatment period. This is not considered an acceptable endpoint for the treatment of ocular inflammation since rebound is a common occurrence after anti-inflammatory drugs are discontinued. This endpoint did not address this concern or the sustainability of the effect after the active-treatment period.*
>
> *The agency requires a more rigorous definition of efficacy which required bromfenac to demonstrate both statistical and clinical significance in the reduction of summed ocular inflammation score, or reduction in anterior cells, as compared to vehicle. A decision was made to redefine the primary efficacy endpoint. The primary efficacy endpoint is defined as the sum of anterior chamber cell and flare equal to zero (based on a five-point scale for each) at Visit 4 (Day 15).*

Regarding the definition of the primary endpoint presented in the NDA submission, the primary medical review (on pages 15-16) reported the following:

> *The primary efficacy outcome was the proportion of subjects in the ITT population with cleared ocular inflammation in the study eye at Visit 4 (Day 15 visit). Cleared ocular inflammation was defined as a summed ocular inflammation score (anterior chamber cell score plus flare score, each measured on a five-point scale) of zero. The anterior chamber cell and flare score was determined as follows:*

Grade	Cell Count	Grade	Flare
0	Non-5 (trace)	0	Complete absence
1	6-15	1	Very slight
2	16-25	2	Moderate
3	26-50	3	Marked
4	>50	4	Intense

Regarding the above cell grade scores, the primary medical review (on page 6) had the following comments:

> *The grading scale used by ISTA to evaluate the clearance of inflammatory cells (component of the primary efficacy endpoint) is not the Division's recommended grading scale. Using the sponsor's scale can lead to misleading results since patients who are graded as having "cleared ocular inflammation" may in fact still have trace inflammatory cells in the anterior chamber. This may or may not have had any clinical relevance based on the types of cells that were present.*

Dr. Wiley Chambers also had concern regarding evaluation of clearance of ocular inflammation allowing presence of non-zero cells in his review dated 03/25/2005 (on page 2):

> *The trials were designed to evaluate the clearance of post-operative inflammation following cataract surgery. Evaluation of clearance in these studies however, was not true clearance because evaluations demonstrating 1-5 cells per high power field (normally called trace inflammation) were counted as cleared.*

According to the blank CRF located at \\fdswa150\NONECTD\N21664\N_000\2004-05-24\CRT\DATASETS\ISTA-BR-CS-001, the chamber cell scores were recorded in the datasets as defined in Table 3.1.1 and the flare scores in Table 3.1.2 (same as in the current NDA203168):

Table 3.1. 1 NDA021664 Xibrom: CRF-defined Anterior Chamber Cell Score

Grade 0	Grade 0.5	Grade 1	Grade 2	Grade 3	Grade 4
0 cell	1-5 cells	6-15 cells	16-25 cells	26-50 cells	> 50 cells

Table 3.1. 2 NDA021664 Xibrom: CRF-defined Anterior Chamber Flare Score

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Complete absence	Very slight (barely detectable)	Moderate (iris and lens clear)	Marked (iris and lens haze)	Intense (fibrin clot)

According to the CRF, the anterior chamber cell counts were graded twice and both grades were recorded on the CRF at each visit. Based on the CRF data, this review conducted analyses for the proportion of subjects whose ocular inflammation was cleared (defined as "0 cell and no flare") and the results are presented in Table 3.1.3 and Table 3.1.4.

The difference between these two analyses is: the analysis in Table 3.1.3 treated all subjects who received a rescue therapy as failures regardless of whether their ocular inflammation was cleared or not, whereas the analysis in Table 3.1.4 did not treat those subjects as failures if their ocular inflammation was cleared a given visit.

Table 3.1. 3 NDA021664 Xibrom: Efficacy Results of Phase 3 Studies (Subjects who received a rescue therapy were treated as failures) (Randomized Population)

Study	Visit	Proportion of Subject with Cleared Ocular Inflammation (0 cell and no flare)		
		Xibrom 0.09% BID	Vehicle BID	Difference (Asymptotic 95% CI)
Study 1	Day 8	64/198(32.3%)	12/98 (12.2%)	20.1 (10.9, 29.3)
	Day 15 (primary)	113/198 (57.1%)	23/98 (23.5%)	33.6 (22.7, 44.5)
Study 2	Day 8	60/158 (38.0%)	11/73 (15.1%)	22.9 (11.7, 34.1)
	Day 15 (primary)	98/158 (62.0%)	23/73 (31.5%)	30.5 (17.4, 43.6)

Data Source: Calculated by the statistical review team based on the submitted efficacy datasets for the Xibrom NDA021664. The submitted datasets are located at \\fdswa150\NONECTD\N21664\N_000\2004-05-24.

Table 3.1. 4 NDA021664 Xibrom: Efficacy Results of Phase 3 Studies (Subjects who received a rescue therapy were treated as successes if their ocular inflammation was cleared)

Study	Visit	Proportion of Subject with Cleared Ocular Inflammation (0 cell and no flare)		
		Xibrom 0.09% BID	Vehicle BID	Difference (%) (Asymptotic 95% CI)
Study 1 (ER)	Day 8	67/198(33.8%)	13/98 (13.3%)	20.6 (11.2, 30.0)
	Day 15 (primary)	124/198 (62.6%)	39/98 (39.8%)	22.8 (11.0, 34.6)
Study 2	Day 8	61/158 (38.6%)	16/73 (21.9%)	16.7 (4.5, 28.8)
	Day 15 (primary)	104/158 (65.8%)	35/73 (47.9%)	17.9 (4.2, 31.5)

Data Source: Same as for Table 3.1.3.

The numbers of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8 but was not cleared at Day 15 are presented in Table 3.1.5. For the two studies combined, there were 19 subjects in both treatment groups whose ocular inflammation was cleared at or prior to Day 8 but was not cleared at Day 15. Among them, 5 (26%) subjects had a cell score of Grade 0.5 (1-5 cells), 3 (16%) subjects had a cell score of Grade 1 (6-15 cells), and the remaining 11 (58%) subjects had a cell score of Grade 0 but a non-zero score for flare. All of these 19 subjects were treated as failures at Day 15 in Table 3.1.3 and Table 3.1.4.

Table 3.1. 5 NDA021664 Xibrom: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8 but was not cleared at Day 15 (cell score or flare score > 0)

Study	Total Number	Cell Score at Day 15					
		Grade 0 (0 cell)	Grade 0.5 (1-5 cells)	Grade 1 (6-15 cells)	Grade 2 (16-25 cells)	Grade 3 (26-50 cells)	Grade 4 (>50 cells)
Study 1	10	6	3	1	0	0	0
Study 2	9	5	2	2	0	0	0
Pooled	19	11	5	3	0	0	0
		Flare Score at Day 15					
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	
Study 1	10	2	8	0	0	0	
Study 2	9	1	7	1	0	0	

Data Source: Same as for Table 3.1.3.

The Clinical Studies section of the drug labeling states that "*the primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing).*" The treatment effects (point estimates) presented in the labeling match the ones presented in Table 3.1.4 for the endpoint of cleared ocular inflammation (0 cell and no flare) at Day 15; thus the treatment effects presented in the labeling are for the proportions of subjects with cleared ocular inflammation (0 cell and no flare) at Day 15. The following is the Clinical Studies section of the drug labeling:

> *Clinical efficacy was evaluated in two randomized, double-masked, placebo-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥ 3 after cataract surgery were assigned to XIBROM or placebo in a 2:1 ratio following surgery. One drop of XIBROM or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant effect of XIBROM on ocular inflammation after cataract surgery was demonstrated (62-66% vs. 40-48%).*

3.2 NDA021862 Nevanac (nepafenac ophthalmic suspension, 0.1% TID) for the treatment of pain and inflammation associated with cataract surgery

This NDA submission was a paper submission and only the datasets were submitted electronically. Thus, the statistical team leader does not have access to the study reports/protocols/analysis plans from this submission. The study designs/analysis plans discussed below are from the primary medical review by Dr. Martin Nevitt dated 07/25/2005 and the primary statistical review by Dr. Karen Qi dated 08/03/2005.

This NDA included two double-masked, randomized, and vehicle controlled phase 3 studies in subjects who underwent cataract extraction with posterior chamber intraocular lens (IOL) implantation. In Study 1, subjects were randomized in a 1:1:1:1:1:1 ratio to six study drugs: nepafenac 0.1% QD, nepafenac 0.1% BID, nepafenac 0.1% TID, vehicle QD, vehicle BID, and

vehicle TID. In Study 2, subjects were randomized in a 1:1 ratio to two study drugs: nepafenac 0.1% TID and vehicle TID. In both studies, one day prior to surgery, subjects self-instilled the randomized study drug into the study (operative) eye, beginning 1 day prior to surgery and continuing on the day of surgery, and through the first 2 weeks of the postoperative period. Ocular inflammation and pain were assessed at the screening visit (1 day to 6 weeks prior to surgery) and each post-surgery visit: Day 1, 3, 7, 14 or early exit visit. Ocular inflammation was evaluated using anterior chamber cell score and flare score. The anterior chamber cell scores and flare scores were defined as follows:

Table 3.2. 1 NDA021862 Nevanac: Anterior Chamber Cell Score

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
0 cell	1-5 cells	6-15 cells	16-30 cells	> 30 cells

Table 3.2. 2 NDA021862 Nevanac: Anterior Chamber Flare Score

Grade 0	Grade 1	Grade 2	Grade 3
No visible flare when compared with the normal eye.	Mild -- flare visible against dark papillary background but not visible against iris background.	Moderate -- flare visible with the slit-lamp beam aimed onto the iris surface as well as the dark papillary background.	Severe -- very dense flare; may also present as a "hazy" appearance of anterior segment structures when viewed with low power magnification of the slit-lamp; present as pronounced Tyndall effect.

In Study 1, the protocol-defined primary endpoint was the proportion of subjects declared as treatment failures, defined as a subject presenting at any postoperative visit with anterior chamber cell score ≥ 3, or flare score ≥ 3, or a pain score ≥ 4. In study 2, the protocol-defined primary endpoint was the proportion of subjects declared as cure at Day 14, defined as the absence (clearance) of ocular inflammation (0 cell and no flare) at Day 14. The medical reviewer agreed with the protocol-defined primary endpoint in Study 2, but did not agree with the protocol-defined primary endpoint in Study 1.

For both studies, this review conducted analysis for the primary endpoint as defined in Study 2, and the results are presented in Table 3.2.3. Of note, the efficacy results for this ocular inflammation endpoint were not included in the Clinical Studies section of the labeling. The study results for the pain endpoint were also presented in Table 2.3.3 as they were included in the Clinical Studies section of the labeling.

Table 3.2. 3 NDA021862 Nevanac: Efficacy Results of Phase 3 Studies (ITT population)

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Nepafenac 0.1% TID	Vehicle TID	Difference (%) (Asymptotic 95% CI)
Study 1*	Day 7	17/56 (30.4%)	6/58 (10.3%)	20.0 (5.6, 34.4)
	Day 14 (**primary**)	26/56 (46.4%)	13/58 (22.4%)	24.0 (7.1, 40.9)

Study 2	Day 7	72/243 (29.6%)	7/233 (3.0%)	26.6 (20.9, 32.8)
	Day 14 **(primary)**	152/243 (62.6%)	40/233 (17.2%)	45.4 (37.6, 53.2)
		Proportion of Subject Who Were Pain Free (0 pain score)		
Study 1	Day 1	45/56 (80.4%)	31/58 (53.4%)	26.9 (10.4, 43.4)
Study 2	Day 1	202/243 (83.1%)	97/233 (41.6%)	41.5 (33.6, 49.4)

Data Source: Calculated by the statistical review team based on the submitted efficacy datasets for NDA021862. The submitted efficacy datasets were obtained from the original statistical reviewer for NDA021862. The ITT population included all randomized subjects who received study drug, completed IOL implant surgery, and returned for at least one post-surgery follow-up visit. Missing data were imputed using LOCF.
* Study results for the QD and BID arms were not presented in this Table.

The numbers of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 7, but was not cleared at Day 14 are presented in Table 3.2.4. For the two studies combined, there were 21 subjects in both treatment groups whose ocular inflammation was cleared at or prior to Day 7 but was not cleared at Day 14. Among them, 17 (81%) subjects had a cell score of Grade 1 (1-5 cells), 3 (14%) subjects had a cell score of Grade 2 (6-15 cells), and 1 (5%) subject had a cell score of Grade 0 and non-zero flare score. All of these 21 subjects were treated as failures at Day 14 in Table 3.2.3.

Table 3.2. 4 NDA021862 Nevanac: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 7 but was not cleared (cell score or flare Score > 0) at Day 14

Study	**Total Number**	**Cell Score at Day 14**				
		Grade 0 (0 cells)	**Grade 1 (1-5 cells)**	**Grade 2 (6-15 cells)**	**Grade 3 (16-30 cells)**	**Grade 4 (>30 cells)**
Study 1	5	1	3	1	0	0
Study 2	16	0	14	2	0	0
Pooled	21	1	17	3	0	0
		Flare Score at Day 14				
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	
Study 1	5	2	2	1	0	
Study 2	16	9	7	0	0	

Data Source: Same for Table 3.2.3.

The Clinical Studies section of the drug labeling does not include any quantitative information about the treatment effect on ocular inflammation, although quantitative data on pain are included. The following is the Clinical Studies section of the drug labeling:

In two double-masked, randomized clinical trials in which patients were dosed three-times-daily beginning one day prior to cataract surgery, continued on the day of surgery and for the

first two weeks of the postoperative period, NEVANAC ophthalmic suspension demonstrated clinical efficacy, compared to its vehicle in treating postoperative inflammation.

Patients treated with NEVANAC ophthalmic suspension were less likely to have ocular pain and measurable signs of inflammation (cells and flare) in the early postoperative period through the end of treatment than those treated with its vehicle.

For ocular pain in both studies a significantly higher percentage of patients (approximately 80%) in the nepafenac group reported no ocular pain on the day following cataract surgery (Day 1) compared to those in the vehicle group (approximately 50%). Results from clinical studies indicated that NEVANAC has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

3.3 NDA022212 Durezol (difluprednate ophthalmic solution, 0.05% QID) for the treatment of inflammation and pain associated with cataract surgery

This NDA included two identically-designed, randomized, and double-masked phase 3 studies in subjects who underwent cataract surgery. One day (Day 1) after surgery, subjects were randomized in a 1:1:1:1 ratio to four study drugs: Durezol BID, Durezol QID, Vehicle BID, and Vehicle QID. On Day 1, study drug was instilled by the investigator/staff, and after Day 1, subjects self-instilled the study drug (Durezol or vehicle) into the study (operative) eye for 14 days, followed by a tapering period of 14 days during which the frequency of the dosage was gradually reduced. Ocular inflammation and pain were assessed at each post-surgery visit: Day 1 (screening/baseline visit), 3, 8, 15, 29, and 1 week after last study dose. The ocular inflammation was evaluated using the anterior chamber cell scores and flare scores defined as follows:

Table 3.3. 1 NDA022212 Durezol: Anterior Chamber Cell Score

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
≤ 1 cell	2-10 cells	11-20 cells	21-50 cells	> 50 cells

Table 3.3. 2 NDA022212 Durezol: Anterior Chamber Flare Score

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None	Mild (trace to clearly noticeable, visible)	Moderate (without plastic aqueous humor)	Marked (with plastic aqueous humor)	Severe (with fibrin deposits and/or clots)

The following is from page 8 of the applicant's final statistical analysis plan (dated on 09/05/2007) regarding the testing approach for the primary and secondary endpoints:

The primary efficacy endpoint is the proportion of subjects with an anterior chamber cell grade of "0" on Day 8 as compared between QID difluprednate and placebo groups. An additional five secondary endpoints will be compared in a hierarchical manner to control the

familywise Type I error. The overall hypothesis testing framework is displayed in the following table.

Primary/first: The proportion of subjects with an anterior chamber cell grade of "0" on Day 8 for QID difluprednate.

Second: The proportion of subjects with an anterior chamber cell grade of "0" on Day 8 for BID difluprednate.

Third: The proportion of subjects with a pain/discomfort score of "0" on Day 3 for QID difluprednate.

Fourth: The proportion of subjects with a pain/discomfort score of "0" on Day 3 for BID difluprednate.

Fifth: The proportion of subjects with an anterior chamber cell grade of "0" on Day 15 for QID difluprednate.

Sixth: The proportion of subjects with an anterior chamber cell grade of "0" on Day 15 for BID difluprednate.

Prioritized hypothesis testing

	Day 3/4		Day 8		Day 15		Day 29	
	QID	BID	QID	BID	QID	BID	QID	BID
Cell grade =" 0"			1st (1)	2nd	5th	6th		
Pain/discomfort score = 0	3rd	4th						

(1) This was the primary endpoint. The secondary endpoints are 2nd, 3rd, etc.

The SAP further states (on page 15) that, *"In general, the method of carrying forward the last post-baseline observation (LOCF) while receiving study medication to the primary endpoint (Day 8) or to Day 15 will be adopted. Specifically, baseline values and values obtained after tapering or rescue with other non-study medications has begun will not be carried forward."*

The primary medical review by Dr. Sonal Wadhwa (dated 06/04/2008) disagreed with the above protocol-defined primary efficacy endpoint and had the following comments (on page 24 of her review):

The primary endpoint of the proportion of subjects with an anterior chamber cell grade of "0" on Day 8 as compared between the ST-601 QID and placebo groups although achieved statistical significance in the 2 trials is not a clinically meaningful endpoint. As was discussed in the comments to the original IND 75,713 and discussed at subsequent meetings, a clinically meaningful endpoint would be complete clearing of anterior chamber cells where a grade 0=0 cells in the anterior chamber.

Thus, in the prioritized hypothesis testing, the endpoint "proportion of subjects with an anterior chamber cell grade of "0" is replaced with the endpoint "proportion of subjects with a cell count of 0". The key efficacy results are summarized in Table 3.3.3.

Table 3.3. 3 NDA022212 Durezol: Applicant's Efficacy Results of Comparing Durezol QID to Vehicle

Study	Visit	Durezol QID	Vehicle BID/QID	Difference (%) (Asymptotic 95% CI)**	P-value*
		Proportion of Subjects with Cleared Ocular Inflammation (cell count of 0)			
Study 1	Day 8	13/55 (23.6%)	11/107 (10.3%)	13.3 (0.7, 26.0)	0.0302
	Day 15	25/55 (45.4%)	15/107 (14.0%)	31.4 (16.7, 46.1)	<0.0001
Study 2	Day 8	11/52 (21.2%)	6/113 (5.3%)	15.8 (4.0, 27.7)	0.0012
	Day 15	19/52 (36.5%)	10/113 (8.8%)	27.7 (13.6, 41.8)	<0.0001
		Proportion of Subject Who Were Pain Free (pain/discomfort score = 0)			
Study 1	Day 3	27/55 (49.1%)	29/107 (27.1%)	22.0 (6.3, 37.7)	0.0026
	Day 8	38/55 (69.1)	32/107 (29.9)	39.2 (24.2, 54.2)	< 0.0001
	Day 15	42/55 (76.4)	47/107 (43.9)	32.4 (17.8, 47.1)	0.0001
Study 2	Day 3	21/52 (40.4%)	25/113 (22.1%)	18.3 (2.9, 33.6)	0.0116
	Day 8	24/52 (46.2)	27/113 (23.9)	22.3 (6.6, 37.9)	0.0027
	Day 15	25/52 (48.1)	29/113 (25.7)	22.4 (6.6, 38.2)	0.0021

Data Source: Table 17 and Table 20 in Applicant's clinical study report for Study 1 and Study 2 from the Durezol NDA022212. *P-value based on Mantel-Haenszel chi-square stratified on study site. **The 95% CI was calculated by the team leader.

From the submitted efficacy datasets for this NDA (\\Cdsesub1\evsprod\NDA022212\0000), the team leader can only locate the data for the subjects in two treatment groups: Durezol BID and Durezol QID; the team leader cannot locate the data for the vehicle-treated subjects. Thus, this review can only reproduce the results presented in Table 3.3.3 for the Durezol QID group. Based on this incomplete efficacy datasets, this review identified 9 Durezol-treated subjects (6 in Study 1 and 3 in Study 2) who had a cell count in the range of 1-5 cells at Day 15 after achieving 0 cell count at or prior to Day 8. These 9 subjects were counted as failures at Day 15 in Table 3.3.3.

The Clinical Studies section of the drug labeling presents the proportion of subjects with complete clearing (defined as a cell count of 0) and the proportion of subjects who were pain free at Day 8 and Day 15 based on the pooled study data. These pooled data are consistent with the numbers in Table 3.3.3. The following is the Clinical Studies section of the drug labeling:

> *Clinical efficacy was evaluated in 2 randomized, double-masked, placebo-controlled trials in which subjects with an anterior chamber cell grade ≥ "2" (a cell count of 11 or higher) after cataract surgery were assigned to DUREZOL or placebo (vehicle) following surgery. One drop of DUREZOL or vehicle was self instilled either 2 times per day or 4 times per day for 14 days, beginning the day after surgery. The presence of complete clearing (a cell count of 0) was assessed 8 and 15 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant benefit was seen in the 4 times per day DUREZOL -treated group in ocular inflammation and reduction of pain when compared with placebo. The consolidated clinical trial results are provided below.*

Ocular Inflammation and Pain Endpoints (Studies Pooled)

	Durezol 4 times per day N = 107		**Vehicle N=220**	
Day	8	15	8	15
Anterior Chamber Cell Clearing (% subjects)	24 (22%)*	44 (41%)*	17 (7%)	25 (11%)
Pain free (% subjects)	62 (58%)*	67 (63%)*	59 (27%)	76 (35%)

*Statistically significantly better than vehicle, $P<0.01$

It should be noted that in addition to the primary of ocular inflammation evaluated on Day 8, the drug labeling also presents the results for the endpoint "proportion of subjects with a cell count of 0 on Day 15", which was the fifth endpoint in the prioritized hypothesis testing procedure. According to the prioritized hypothesis testing procedure defined in the SAP, this endpoint could be tested only if the test for the fourth endpoint "proportion of subjects with 0 pain/discomfort score on Day 3 for Durezol BID was statistically significant. As shown in Table 3.3.4, the test for this fourth endpoint was not statistically significant: p-value = 0.0772 for Study 1 and p-value = 0.0800 for Study 2. Thus, following the prioritized hypothesis testing procedure, the endpoint (fifth endpoint) of proportion of subjects with a cell count of 0 on Day 15 for Durezol QID should not be tested. No rationale was provided in either the medical or statistical reviews to explain why these results were presented in the labeling. This reviewer believes that these results are presented in the labeling because they help prescribing physician and patients better understand the treatment effects of Durezol on ocular inflammation.

It should also be noted that the drug labeling does not present the results for the pain free endpoint at Day 3, which was the third endpoint in the prioritized hypothesis testing procedure; instead, the labeling presents the results for the pain free endpoint at Day 8 and Day 15, which were not in the list of the pre-defined primary/secondary endpoints and were included in the list of more than 20 exploratory endpoints. No rationale was provided in either the medical or statistical reviews to explain why these results were presented in the labeling. This reviewer

believes that these results are presented in the labeling because they help prescribing physician and patients better understand the treatment effects of Durezol on ocular pain.

In summary, this drug labeling is an example where the presented efficacy results for some endpoints are not adjusted for multiplicity according to the pre-defined prioritized hypothesis testing procedure.

Table 3.3. 4 NDA022212 Durezol: Applicant's Efficacy Results of Comparing Durezol BID to Vehicle

Study	Visit	Durezol BID	Vehicle BID/QID	Difference (%) (Asymptotic 95% CI)*	P-value
		Proportion of Subjects with Cleared Ocular Inflammation (cell count of 0)			
Study 1	Day 8	9/57 (15.8)	11/107 (10.3)	5.5 (-5.6, 16.6)	0.3584
	Day 15	25/57 (43.9)	15/107 (14.0)	29.8 (15.4, 44.3)	<0.0001
Study 2	Day 8	10/53 (18.9)	6/113 (5.3)	13.6 (2.2, 24.9)	0.0075
	Day 15	20/53 (37.7)	10/113 (8.8)	28.9 (14.8, 42.9)	<0.0001
		Proportion of Subject Who Were Pain Free (pain/discomfort score = 0)			
	Day 3	23/57 (40.4)	29/107 (27.1)	13.2 (-2.0, 28.5)	0.0772
Study 1	Day 8	23/57 (40.4)	32/107 (29.9)	10.4 (-5.0, 25.9)	0.2250
	Day 15	36/57 (63.2)	47/107 (43.9)	19.2 (3.6, 34.9)	0.0209
	Day 3	19/53 (35.8)	25/113 (22.1)	13.7 (-1.3, 28.7)	0.0800
Study 2	Day 8	23/53 (43.4)	27/113 (23.9)	19.5 (4.0, 35.0)	0.0121
	Day 15	23/53 (43.4)	29/113 (25.7)	17.7 (2.1, 33.3)	0.0150

Data Source: Same as in Table 3.3.3.

3.4 NDA021664 Bromday (bromfenac ophthalmic solution, 0.09% QD) for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction

This NDA included three phase 3 studies in subjects who underwent cataract extraction with posterior chamber intraocular lens implantation. Subjects were randomized in a 1:1 ratio to two study drugs (bromfenac or vehicle) 1 day prior to surgery. Subjects instilled study drug into the study (operative) eye once daily beginning 1 day prior to surgery, continued on the day of

surgery and through the first 14 days post-surgery. Ocular inflammation and pain were assessed at the screening visit (1 to 8 days prior to surgery) and each post-surgery visit: Day 1, 3, 8, 15, 22 (or 7 days after last dose of study drug if discontinued the study drug prematurely). The ocular inflammation was evaluated using anterior chamber cell score and flare score. The anterior chamber cell scores and flare scores were defined in the same way as the ones presented in the current NDA203168. The definition for the primary efficacy endpoint and the secondary endpoint was the same for all three studies. The secondary efficacy endpoint was pain free at Day 1. Regarding the primary efficacy endpoint of cleared ocular inflammation, the applicant's analysis plan for Study 3 (dated on 01/12/2009 pages 6-7) states the following:

The primary efficacy outcome of cleared ocular inflammation is defined as the proportion of subjects that achieve a summed ocular inflammation score (SOIS) of grade 0 (0 cells and absence of flare) by Day 15. The SOIS is defined as the sum of the mean anterior chamber cells score and anterior flare score. The anterior chamber cell grade is determined twice per study visit, and is based on a manual count of cells using a slit lamp biomicroscopy. Between the two manual cell counts, the biomicroscopy is to be refocused off and back onto the anterior chamber, as a means of obtaining a more precise average estimate. The anterior chamber cell grade and flare grade are determined as follows:

Anterior Chamber Cells			**Anterior Chamber Flare**	
Grade	**Manual Cell Count**	**Recorded Cell Grade**	**Grade**	**Flare**
0	0	0	0	Complete absence
0.5	1-5 (trace)	0.5	1	Very slight (barely detectable)
1	6-15	1	2	Moderate (iris and lens clear)
2	16-25	2	3	Marked (iris and lens hazy)
3	26-50	3	4	Intense (fibrin clot)
4	>50	4		

The anterior chamber cell score at each study visit is defined as the average of both cell grades obtained. If only one grade was collected for any given visit, the cell score will be set to the single cell grade. An anterior chamber cell score of zero is achieved at any given study visit only if both cell grades are zero, or if only a single cell grade is recorded and was observed to be zero. In order to satisfy the primary endpoint of a SOIS of grade zero by Day 15, an anterior chamber cells score of grade zero and an anterior flare score of grade zero must be observed on any scheduled visit on or prior to the Day 15 visit.

Regarding the method of handling missing data, the SAP (page 13) states the following:

Two types of missing values are anticipated: 1) from subjects who are not responding to investigational product treatment (based on assessment of ocular inflammation and ocular

pain) and who may require alternative medical management (i.e., rescue therapy) and 2) from subjects who miss scheduled evaluations but continue on investigational product treatment during the study. For the first type of missing data, those subjects who receive a rescue medication prior to Day 15, the observed outcome nearest (on or before) the date of receiving rescue medication will be carried forward and used in the determination of the missing outcome. For the second type of missing data, the outcome from the last visit at which it was measured will be carried forward.

The applicant's analysis results of the primary and secondary endpoints are presented in Table 3.4.1.

Table 3.4. 1 NDA021664 Bromday: Applicant's Efficacy Results of Phase 3 Studies (ITT Population)

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Bromday 0.09% QD	**Vehicle QD**	**Difference (%) (Asymptotic 95% CI)**
Study 1	Day 8	20/63 (31.7%)	15/63 (23.8%)	7.9 (-7.6, 23.5)
	Day 15 (primary)	28/63 (44.4%)	20/63 (31.7%)	12.7 (-4.1, 29.5)
Study 2	Day 8	19/75 (25.3)	14/75 (18.7)	6.7 (-6.5, 19.9)
	Day 15 (primary)	35/75 (46.7)	22/75 (29.3)	17.3 (2.0, 32.6)
Study 3	Day 8	36/152 (23.7%)	23/147 (15.6%)	8.0 (-0.9, 17.0)
	Day 15 (primary)	70/152 (46.1%)	36/147 (24.5%)	21.6 (11.0, 32.1)
		Proportion of Subject Who Were Pain Free (0 pain score)		
Study 1	Day 1	51/63 (81.0%)	46/63 (73.0%)	7.9 (-6.7, 22.6)
Study 2	Day 1	65/78 (83.3%)	40/78 (51.3%)	32.1(18.2, 45.9)
Study 3	Day 1	135/152 (88.8%)	105/147 (71.4%)	17.4 (8.5, 26.2)

Data Source: Calculated by the statistical review team based on the submitted efficacy data for NDA021664 Bromday. ITT population included all randomized subjects (in study 2, six subjects from one study site were excluded due to data integrity issues; for details see page 8 of the primary medical review).

The primary endpoint in this application was analyzed in the same way as the current NDA203168; As discussed below, the applicant's analysis in Table 3.4.1 treated subjects whose ocular inflammation was cleared at or prior to Day 8, but was subsequently not cleared at Day 15 as successes by Day 15.

As shown in Table 3.4.2, for the three studies combined, there were 24 subjects in both treatment groups whose ocular inflammation was cleared at or prior to Day 8, but was not cleared at Day 15. Among them, 16 (67%) subjects had a cell score of Grade 0.5 (1-5 cells), 5 (21%) subjects had a cell score of Grade 1 (6-15 cells), 1 (4%) subject had a cell score of Grade 2 (16-25 cells),

1 (4%) subject had a cell score of Grade 4 (>50 cells), and 1 (4%) subject had a cell score of Grade 0 but a non-zero score for flare. This review found that all of these 24 subjects were considered as successes "by Day 15" in the applicant's analysis in Table 3.4.1

As shown in Table 3.4.3, if these subjects were counted as failures at Day 15, the success rate of having cleared ocular inflammation would decrease 4.7% in both treatment groups for Study 1, 1.4% in the Bromday group and 4.0% in the vehicle group for Study 2, and 4.0% in the Bromday group and 6.1% in the vehicle group for Study 3.

Table 3.4. 2 NDA021664 Bromday: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8 but was not cleared (cell score or flare score > 0) at Day 15

Study	Total Number	Cell Score at Day 15					
		Grade 0 (0 cell)	Grade 0.5 (1-5 cells)	Grade 1 (6-15 cells)	Grade 2 (16-25 cells)	Grade 3 (26-50 cells)	Grade 4 (>50 cells)
Study 1	6	1	3*	2	0	0	0
Study 2	3	0	2	0	0	0	1
Study 3	15	0	11	3	1	0	0
Pooled	24	1	16	5	1	0	1
		Flare Score at Day 15					
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	
Study 1	6	1	4	0	0	1	
Study 2	3	3	0	0	0	0	
Study 3	15	7	8	0	0	0	

Data Source: Same as for Table 3.4.1. *One subject had "0" cell score for the first grade and "0.5" cell score for the second grade and 2 subjects had "0.5" cell score for both grades.

Table 3.4. 3 NDA021664 Bromday: FDA's Analysis Results of Phase 3 Studies

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Bromday 0.09% QD	Vehicle QD	Difference (%) (Asymptotic 95% CI)
Study 1	Day 8	20/63 (31.7%)	13/63 (20.6%)	11.1 (-4.1, 26.3)
	Day 15 (primary)	25/63 (39.7%)	17/63 (27.0%)	12.7 (-3.6, 29.0)
Study 2	Day 8	18/75 (24.0)	11/75 (14.7)	9.3 (-3.2, 21.9)
	Day 15 (primary)	34/75 (45.3)	19/75 (25.3)	20.0 (5.0, 35.0)
Study 3	Day 8	34/152 (22.4%)	20/147 (13.6%)	8.8 (0.1, 17.4)
	Day 15 (primary)	64/152 (42.1%)	27/147 (18.4%)	23.7 (13.7, 33.8)

Data Source: Same as for Table 3.4.1.

The point estimates for the primary endpoint in Table 3.4.1 for Study 2 and Study 3 are presented in the drug labeling for Bromday. The Clinical Studies section of the drug labeling states that, "The primary endpoint was clearing of ocular inflammation by day 15." As discussed above, subjects whose ocular inflammation was cleared at or prior to Day 8 but was not cleared at Day 15 were treated as successes "by day 15" in Table 3.4.1. The analysis of this primary endpoint in the Bromday (bromfenac 0.09% QD) NDA (by ISTA) is similar to the analysis in the current NDA203168 for Prolensa (bromfenac 0.07% QD) (this NDA was originally submitted by ISTA and now owned by Bausch and Lomb). The following is the Clinical Studies section of the drug labeling for Bromday:

Clinical efficacy was evaluated in three randomized, double-masked, placebo-controlled trials in which subjects requiring cataract surgery were assigned to Bromday or placebo. Patients were dosed with one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. An additional efficacy endpoint was the number of patients who were pain free on day 1 after cataract surgery.

In 2 of the 3 studies, Bromday ophthalmic solution had statistically significant higher incidence of completely clearing inflammation (46-47% vs. 25-29%) and also had a statistically significant higher incidence of subjects that were pain free at day 1 post cataract surgery (83-89% vs. 51-71%).

3.5 NDA200738 Lotemax (loteprednol etabonate ophthalmic ointment, 0.5% QID) for the treatment of postoperative inflammation and pain following ocular surgery

This NDA included two identically-designed, double-masked, randomized, and vehicle controlled phase 3 studies in subjects who underwent cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation. Subjects were randomized in a 1:1 ratio to two study drugs (Lotemax ointment or vehicle) on Day 1 after surgery. Starting on Day 1, subjects self-administered approximately one-half inch long ribbon of study drug to the lower cul-de-sac of the study (operative) eye, four times daily (QID), at approximately four hour intervals for 14 days. Ocular inflammation and pain were assessed at the screening visit (within 14 days prior to surgery) and each post-surgery visit: Day 1, 3, 8, 15, and 18. Ocular inflammation was evaluated using anterior chamber cell score and flare score. The anterior chamber cell scores were defined in the same way as in Table 3.2.1 for Nevanac NDA021862. The anterior chamber flare scores were defined as follows:

Table 3.5. 1 NDA200738 Lotemax Ointment: Anterior Chamber Flare Score

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
None; No Tyndall effect.	Mild; Tyndall effect barely discernible.	Moderate; Tyndall effect in anterior chamber is moderately intense. Iris pattern is seen clearly.	Severe; Tyndall effect in anterior chamber is severely intense. Iris pattern cannot be seen clearly.	Very severely dense. The aqueous has a white and milky appearance.

There were two primary endpoints: cleared ocular inflammation (0 cell and no flare) at Day 8 and pain free at Day 8. These two endpoints were tested hieratically: first for cleared ocular inflammation and then pain free. Missing data and subjects who received rescue therapy were treated as failures in the primary analysis of the endpoints. The key efficacy results are summarized in Table 3.5.2.

Table 3.5. 2 NDA200738 Lotemax Ointment: Efficacy Results of Phase 3 Studies (ITT Population)

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Lotemax Ointment	**Vehicle**	**Difference (%) (Asymptotic 95% CI)**
Study 1	Day 8 (**primary**)	48/201 (23.9%)	27/199 (13.6%)	10.3 (2.7, 17.3)
	Day 15	84/201 (41.8%)	30/199 (15.1%)	26.7 (18.3, 35.2)
Study 2	Day 8 (**primary**)	64/203 (31.5%)	23/202 (11.4%)	20.1 (12.4, 27.9)
	Day 15	107/203 (52.7%)	42/202 (20.8%)	31.9 (23.1, 40.8)
		Proportion of Subject Who Were Pain Free (0 pain score)		
Study 1	Day 8	156/201 (77.6%)	90/199 (45.2%)	32.4 (23.4, 41.4)
Study 2	Day 8	149/203 (73.4%)	83/202 (41.1%)	32.3 (23.2, 41.9)

Data Source: Calculated by the statistical review team based on the submitted efficacy datasets for NDA200738. The ITT population included all randomized subjects.

The numbers of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8 but was not cleared at Day 15 are presented in Table 3.5.3. For the two studies combined, there were 33 subjects in both treatment groups whose ocular inflammation was cleared at or prior to Day 8 but was not cleared at Day 15. Among them, 18 (55%) subjects had a cell score of Grade 1 (1-5 cells), 3 (9%) subjects had a cell score of Grade 2 (6-15 cells), 2 (6%) subjects had a cell score of Grade 3 (16-30 cells), and 10 (30) subjects had Grade 0 cell score but non-zero flare score. All of these 33 subjects were treated as failures at Day 15 in Table 2.5.2 and the success rate (point estimates) at Day 8 are included in the approved labeling.

Table 3.5. 3 NDA200738 Lotemax Ointment: Number of subjects whose ocular inflammation was cleared (0 cell count and no flare) at or prior to Day 8 but was not cleared (cell score or flare score > 0) at Day 15

Study	Total Number	Cell Score at Day 15				
		Grade 0 (0 cell)	**Grade 1 (1-5 cells)**	**Grade 2 (6-15 cells)**	**Grade 3 (16-30 cells)**	**Grade 4 (>30 cells)**
Study 1	14	4	8	1	1	0
Study 2	19	6	10	2	1	0
Pooled	33	10	18	3	2	0

		Flare Score at Day 15				
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Study 1	14	10	4	0	0	0
Study 2	19	7	10	1	1	0

Data Source: Same as for Table 2.5.2.

The Clinical Studies section of the drug labeling presents the point estimates for the primary endpoints at Day 8. These point estimates match the results in Table 3.5.2. The following is the Clinical Studies section of the drug labeling:

> *In two independent, randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 805 subjects meeting a protocol-specified threshold amount of anterior chamber inflammation, LOTEMAX ointment was more effective compared to its vehicle for complete resolution of post-operative anterior chamber cell, flare, and pain following cataract surgery. Primary endpoint was complete resolution of anterior chamber cells and flare (cell count of 0 and no flare) and no pain at post-operative day 8. The individual clinical trial results are provided below.*
>
> *In the 2 studies, Lotemax had statistically significant higher incidence of completely clearing of anterior chamber cells and flare at post-operative day 8 (24-32% vs. 11-14%) and also had a statistically significant higher incidence of subjects that were pain free at post-operative day 8 (73-78% vs. 41-45%).*

As presented in the next section for the Lotemax gel NDA, the primary endpoint of cleared ocular inflammation was defined as achieving 0 cell, instead of achieving 0 cell and 0 flare score as in the Lotemax ointment NDA. For comparison purpose, the results for the endpoint of achieving 0 cell are presented in Table 3.5.4 for Lotemax ointment NDA. The results in Table 3.5.2 and Table 3.5.4 show that the endpoint of achieving 0 cell and 0 flare score is mainly driven by the endpoint of achieving 0 cell.

Table 3.5. 4 NDA200738 Lotemax Ointment: Efficacy Results of Phase 3 Studies for the Endpoint of Achieving 0 Cell

Study	**Visit**	**Proportion of Subjects with Cleared Ocular Inflammation (0 cell)**		
		Lotemax Ointment	**Vehicle**	**Difference (%) (Asymptotic 95% CI)**
Study 1	Day 8 (**primary**)	49/201 (24.4%)	27/199 (13.6%)	10.8 (2.7, 18.9)
	Day 15	87/201 (43.3%)	30/199 (15.1%)	28.2 (19.2, 37.2)
Study 2	Day 8 (**primary**)	69/203 (34.0%)	24/202 (11.9%)	22.1 (13.7, 30.5)
	Day 15	108/203 (53.2%)	48/202 (23.8%)	29.4 (19.9, 39.0)

Data Source: Table 14.2.3.2 from the applicant's CSR in both Study 1 and Study 2.

3.6 NDA202872 Lotemax (loteprednol etabonate ophthalmic gel, 0.5% QID) for the treatment of postoperative inflammation and pain following ocular surgery

This NDA included two identically-designed, double-masked, randomized, and vehicle-controlled phase 3 studies in subjects who underwent cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation. Subjects were randomized in a 1:1 ratio to two study drugs (Lotemax gel or vehicle) on Day 1 after surgery. Starting on Day 1, subjects self-instilled one or two drops of study drug into the study (operative) eye four times a day (QID) at approximately four hour intervals for 14 days. Ocular inflammation and pain were assessed at the screening visit (within 14 days prior to surgery) and each post-surgery visit: Day 1, 3, 8, 15, and 18. The ocular inflammation was evaluated using anterior chamber cell score and flare score. The anterior chamber cell scores and flare scores were defined in the same way as in NDA200738 for Lotemax ointment (the cell score was the same as in Table 3.2.1 for Nevanac NDA021862). There were two primary endpoints: cleared ocular inflammation (0 cell) at Day 8 and pain free at Day 8. These two endpoints were tested hieratically: first for cleared ocular inflammation and then pain free. Missing data and subjects who received rescue therapy were treated as failures in the primary analysis of the endpoints. The key efficacy results are summarized in Table 3.6.1.

Table 3.6. 1 NDA202872 Lotemax Gel: Efficacy Results of Phase 3 Studies (ITT Population)

		Proportion of Subjects with Cleared Ocular Inflammation (0 cell)		
Study	**Visit**	**Lotemax Gel**	**Vehicle**	**Difference (%) (Asymptotic 95% CI)**
Study 1	Day 8 (primary)	62/203 (30.5%)	33/203 (16.3%)	14.3 (6.2, 22.4)
	Day 15	102/203 (50.2%)	44/203 (21.7%)	28.6 (19.7, 37.5)
Study 2	Day 8 (primary)	64/206 (31.1%)	28/201 (13.9%)	17.1 (9.2, 25.1)
	Day 15	116/206 (56.3%)	61/201 (30.3%)	26.0 (16.7, 35.3)
		Proportion of Subject Who Were Pain Free (0 pain score)		
Study 1	Day 8	148/203 (72.9%)	85/203 (41.9%)	31.0 (21.9, 40.2)
Study 2	Day 8	156/206 (75.7%)	92/201 (45.8%)	30.0 (20.9, 39.0)

Data Source: Calculated by the statistical review team based on the submitted efficacy datasets for NDA202872. The ITT population included all randomized subjects.

As shown in Table 3.6.2, for the two studies combined, there were 31 subjects whose ocular inflammation was cleared at or prior to Day 8 but was not cleared at Day 15. Among them, 27 (87%) subjects had a cell scores rebounded to Grade 1 (1-5 cells), 3 (10%) subjects' cell scores rebounded to Grade 2 (6-15 cells), and 1 (3%) subject' cell score rebounded to Grade 4 (>30 cells). All of these 31 subjects were treated as failures at Day 15 in Table 3.6.1.

Table 3.6. 2 NDA202872 Lotemax Gel: Number of subjects whose ocular inflammation was cleared (0 cell) at or prior to Day 8 but was not cleared (cell score > 0) at Day 15

Study	Total Number	Cell Score at Day 15				
		Grade 0 (0 cell)	Grade 1 (1-5 cells)	Grade 2 (6-15 cells)	Grade 3 (16-30 cells)	Grade 4 (>30 cells)
Study 1	16	0	13	2	0	1
Study 2	15	0	14	1	0	0
Pooled	31	0	27	3	0	1

Data Source: Same as in Table 3.6.1.

The Clinical Studies section of the drug labeling presents the point estimates for the primary endpoints at Day 8. These point estimates match the results in Table 3.6.1. The following is the Clinical Studies section of the drug labeling for Lotemax Gel:

> *In two randomized, multicenter, double-masked, parallel-group, vehicle-controlled studies in 813 subjects with, post-operative inflammation, LOTEMAX was more effective compared to its vehicle in resolving anterior chamber inflammation and pain following cataract surgery. Primary endpoints were complete resolution of anterior chamber cells (cell count of 0) and no pain at post-operative day 8. In these studies, LOTEMAX had a statistically significant higher incidence of subjects with complete clearing of anterior chamber cells (31% vs. 14-16%) and were pain free at post-operative day 8 (73-76% vs. 42-46%).*

As noticed earlier, the primary endpoint of cleared ocular inflammation in this Lotemax gel NDA is different from the one in the Lotemax ointment NDA200738 in that it only requires achieving 0 cell regardless of the flare score, whereas the Lotemax ointment NDA requires achieving 0 cell and 0 flare score. For comparison purpose, the efficacy results for the endpoint of achieving 0 cell and 0 flare score are presented in Table 3.6.3 for the Lotemax gel NDA. The results in Table 3.6.1 and Table 3.6.3 show that the endpoint of achieving 0 cell and 0 flare score is mainly driven by the endpoint of achieving 0 cell.

Table 3.6. 3 NDA202872 Lotemax Gel: Efficacy Results of Phase 3 Studies for the Endpoint of Achieving 0 Cell and 0 Flare Score

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and 0 flare score)		
		Lotemax Gel	Vehicle	Difference (%) (Asymptotic 95% CI)
Study 1	Day 8 (primary)	60/203 (29.6%)	33/203 (16.3%)	13.3 (4.7, 21.9)
	Day 15	101/203 (49.8%)	44/203 (21.7%)	28.1 (18.7, 37.5)
Study 2	Day 8 (primary)	63/206 (30.6%)	23/201 (11.4%)	19.1 (11.0, 27.3)
	Day 15	115/206 (55.8%)	57/201 (28.4%)	27.5 (17.8, 37.2)

Data Source: Table 14.2.3.3 from the applicant's CSR in both Study 1 and Study 2.

3.7 NDA203491 Ilevro (nepafenac ophthalmic suspension, 0.3% QD) for the treatment of pain and inflammation associated with cataract surgery

This NDA included two double-masked, randomized, vehicle and active-controlled phase 3 studies in subjects who underwent cataract extraction by phacoemulsification with posterior chamber intraocular lens (IOL) implantation. Randomization occurred at the screening/baseline visit (2 days to 6 weeks prior to surgery). In Study 1, subjects were randomized in a 4:4:1:1 ratio to four study drugs: nepafenac 0.3% QD, nepafenac 0.1% TID (Nevanac, approved in NDA021862), vehicle of nepafenac 0.3% QD, and vehicle of nepafenac 0.1% TID. In Study 2, subjects were randomized in a 2:2:1 ratio to three study drugs: nepafenac 0.3% QD, nepafenac 0.1% QD, and vehicle of nepafenac 0.3% QD. Subjects self-instilled study drug into the study (operative) eye, beginning 1 day prior to surgery and continuing on the day of surgery, and for 14 days following surgery.

Ocular inflammation and pain were assessed at screening/baseline visit (2 days to 6 weeks prior to surgery) and each post-surgery visit: Day 1, 3, 7, 14 (or early exit). Ocular inflammation was evaluated using anterior chamber cell score and flare score. The anterior chamber cell scores and flare scores were defined in the same way as NDA021862 for Nevanac, Table 3.2.1 and Table 3.2.2. The primary endpoint was cleared ocular inflammation (0 cell and no flare) at Day 14. The secondary endpoint was complete resolution of pain at Day 14. Subjects who received a rescue therapy were treated as failures and missing data were imputed using LOCF method in the primary analysis. The key efficacy results for nepafenac 0.3% QD and its vehicle are summarized in Table 3.7.1.

Table 3.7. 1 NDA203491 Ilevro: Efficacy Results of Phase 3 Studies (Randomized Population)

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell count and 0 flare score)		
		Nepafenac 0.3% QD	**Vehicle QD**	**Difference (Asymptotic 95% CI)**
Study 1	Day 7	275/851(32.3%)	37/211 (17.5%)	14.8 (8.8, 20.8)
	Day 14 (**primary**)	552/851 (64.9%)	67/211 (31.8%)	33.1 (26.1, 40.2)
Study 2	Day 7	160/540 (29.6%)	26/268 (9.7%)	19.9 (14.7, 25.2)
	Day 14 (**primary**)	331/540 (61.3%)	63/268 (23.5%)	37.8 (31.3, 44.3)
		Proportion of Subject who Were Pain Free (0 pain score)		
Study 1	Day 14	734/851 (86.3%)	98/211 (46.4%)	39.8 (32.7, 46.9)
Study 2	Day 14	456/540 (84.4%)	101/268 (37.7%)	46.8 (40.2, 53.3)

Data Source: Calculated by the statistical review team based on the submitted efficacy datasets for NDA203491.

The numbers of subjects whose ocular inflammation was cleared (0 cell count and no flare) at or prior to Day 7 but was not cleared at Day 14 are presented in Table 3.7.2. For the two studies combined, there were 146 subjects in both treatment groups whose ocular inflammation was cleared at or prior to Day 7 but was not cleared (cell score or flare score > 0) at Day 14. Among them, 111 (76%) subjects had a cell score of Grade 1 (1-5 cells), 20 (14%) subjects had a cell score of Grade 2 (6-15 cells), 7 (5%) subjects had a cell score of Grade 3 (16-30 cells), 1 (1%) subject had a cell score of Grade 4 (>30 cells), and 7 (5%) subjects had a Grade 0 cell score but non-zero flare score. All of these 146 subjects were considered as failures at Day 14 in Table 3.7.1, and the success rates at Day 14 in Table 3.7.1 were included in the approved labeling.

Table 3.7. 2 NDA203491 Ilevro: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 7 but was not cleared (cell score or flare score > 0) at Day 14

Study	Total Number	Cell Score at Day 14				
		Grade 0 (0 cells)	Grade 1 (1-5 cells)	Grade 2 (6-15 cells)	Grade 3 (16-30 cells)	Grade 4 (>30 cells)
Study 1	80	4	61	9	5	1
Study 2	66	3	50	11	2	0
Pooled	146	7	111	20	7	1
		Flare Score at Day 14				
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	
Study 1	80	50	26	4	0	
Study 2	66	45	16	4	1	

Data Source: Same as for Table 3.7.1.

The Clinical Studies section of the drug labeling states that the nepafenac 0.3% QD treatment effect over vehicle for resolution of inflammation was significantly better than vehicle in both studies at day 7 and day 14 post-surgery; however, the labeling only presents the study results (including point estimates and 95% CI) at day 14, and the labeling does not define "resolution of inflammation". The following is the Clinical Studies section of the drug labeling for Ilevro:

> *In two double masked, randomized clinical trials in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, ILEVRO™ (nepafenac ophthalmic suspension), 0.3% demonstrated superior clinical efficacy compared to its vehicle in treating postoperative pain and inflammation. Treatment effect over vehicle for resolution of ocular pain occurred as early as day 1 post-surgery. Treatment effect over vehicle for resolution of inflammation was significantly better than vehicle in both studies at day 7 and day 14 post-surgery.*

Inflammation and Ocular Pain Resolution Results of Nepafenac ophthalmic suspension, 0.3% versus Vehicle at Day 14 Post-surgery (All-Randomized Population)

Studies	Treatment	Inflammation Resolution at Postop Day 14	Ocular Pain Resolution at Postop Day 14
Study 1	Nepafenac ophthalmic suspension, 0.3% (n/N) [(1)]	552/851 (65%)	734/851 (86%)

	NEVANAC (n/N) [1]	568/845 (67%)	737/845 (87%)
	Vehicle (n/N) [1]	67/211 (32%)	98/211 (46%)
	Difference (95% CI) [2]	33% (26%, 40%)	40% (32%, 47%)
Study 2	Nepafenac ophthalmic suspension, 0.3% (n/N) [1]	331/540 (61%)	456/540 (84%)
	Vehicle (n/N) [1]	63/268 (24%)	101/268 (38%)
	Difference (95% CI) [2]	38% (31%, 45%)	47% (40%, 54%)

[1] n/N is the ratio of those with complete resolution of anterior chamber cell and flare by the postoperative day 14 visit over all randomized subjects. [2] Difference is (Nepafenac ophthalmic suspension, 0.3% – vehicle). The 95% confidence interval is derived using asymptotic approximation.

3.8 Summary of Findings on the 7 Approved NDAs

3.8.1 Varied anterior chamber cell grade scores and flare scores were used to evaluate ocular inflammation

Ocular inflammation after cataract surgery was evaluated using anterior chamber cell score and flare score in the 7 approved NDAs. Three different approaches (Table 3.8.1) that were agreed upon or recommended by the medical reviewers were utilized in defining anterior chamber cell grade scores in these NDAs. Except Grade 0 (means 0 cell), the definitions of the non-zero cell grade scores appear quite arbitrary; for example, Grade 0.5 in the current NDA203168 is the same as Grade 1 in NDA203491, and Grade 1 in the current NDA203168 is the same as Grade 2 in NDA203491, and Grade 4 could mean more than 30 cells or more than 50 cells. Thus, if the definition of the cell grade scores is not provided in drug labeling, one should avoid using non-zero cell grade scores to describe the treatment effect on ocular inflammation in drug labeling.

Table 3.8. 1: Anterior Chamber Cell Grade Scores in 7 Approved NDAs

	Grade 0	Grade 0.5	Grade 1	Grade 2	Grade 3	Grade 4
Current NDA203168 NDA021664 Bromday NDA021664 Xibrom*	0 cell	1-5 cells	6-15 cells	16-25 cells	26-50 cells	> 50 cells
NDA203491 Ilevro NDA021862 Nevanac NDA202872 Lotemax NDA200738 Lotemax	0 cell	NOT USED	1-5 cells	6-15 cells	16-30 cells	> 30 cells
NDA022212 Durezol**	0 cell	NOT USED	1-10 cells	11-20 cells	21-50 cells	> 50 cells

*Study protocols defined Grade 0 as "≤5 cells", FDA medical reviewer disagreed and recommended defining Grade 0 as "0 cell"; the CRF collected data as defined in the table.

**Stud protocols defined Grad 0 as "≤1 cell", FDA medical reviewer disagreed and recommended defining Grade 0 as "0 cell"; the CRF collected the exact cell count data (0, or 1) when cell count was ≤1, allowing cell grade score re-defined as in the table.

As shown in Table 3.8.2, four different approaches, one for each drug regardless of the formulation/dosing frequency, were utilized in defining anterior chamber flare scores in these

NDAs. Two NDAs (Ilevro and Nevanac) used a 4-point scale and the other NDAs used a 5-point scale. For all these NDAs, the definitions of Grade 0 were consistent, indicating absence of flare; while the definitions of Grade 1 (indicating mild flare) and Grade 2 (indicating moderate flare) seem also consistent, the definitions of Grade 3 and Grade 4 were overlapped. Thus, if the definition of the flare scores is not provided in drug labeling, one should avoid using non-zero flare scores to describe the treatment effect on ocular inflammation in drug labeling.

Table 3.8. 2: Anterior Chamber Cell Flare Scores in 7 Approved NDAs

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Current NDA203168 NDA021664 Bromday NDA021664 Xibrom	Complete absence	Very slight (barely detectable)	Moderate (iris and lens clear)	Marked (iris and lens haze)	Intense (fibrin clot)
NDA203491 Ilevro NDA021862 Nevanac	No visible flare when compared with the normal eye	Mild (flare visible against dark papillary background but not visible against iris background)	Moderate (flare visible with the slit-lamp beam aimed onto the iris surface as well as the dark papillary background)	Severe (very dense flare; may also present as a "hazy" appearance of anterior segment structures when viewed with low power magnification of the slit-lamp; present as pronounced Tyndall effect)	NOT USED
NDA202872 Lotemax NDA200738 Lotemax	None; No Tyndall effect.	Mild; Tyndall effect barely discernible.	Moderate; Tyndall effect in anterior chamber is moderately intense. Iris pattern is seen clearly.	Severe; Tyndall effect in anterior chamber is severely intense. Iris pattern cannot be seen clearly.	Very severely dense. The aqueous has a white and milky appearance.
NDA022212 Durezol	None	Mild (trace to clearly noticeable, visible)	Moderate (without plastic aqueous humor)	Marked (with plastic aqueous humor)	Severe (with fibrin deposits and/or clots)

3.8.2 Varied definitions were used to define "cleared ocular inflammation"

The definitions of "cleared ocular inflammation" varied in these NDAs. As shown in Table 3.8.3, the two definitions that were agreed upon or recommended by the medical reviewers are: (1) achieving "0 cell and no flare" in 5 applications, and (2) achieving "0 cell" in 2 applications (Durezol NDA and Lotemax gel NDA).

Table 3.8. 3: Definitions of Cleared Ocular Inflammation in 7 Approved NDAs

Current NDA203168	Same as Bromday
NDA021664 Bromday	0 cell and no flare
NDA021664 Xibrom	Protocol-defined as "cell score + flare score ≤ 1"; FDA medical reviewer disagreed – revised to 0 cell and no flare

NDA202872 Lotemax	0 cell
NDA200738 Lotemax	0 cell and no flare
NDA203491 Ilevro	0 cell and no flare
NDA021862 Nevanac	0 cell and no flare
NDA022212 Durezol	Protocol-defined as "≤ 1 cell"; FDA medical reviewer disagreed – changed to 0 cell

3.8.3 Every Approved NDA had subjects whose ocular inflammation was cleared by week 1 (days 7-8) but was not cleared at week 2 (days 14-15) post-surgery

As shown in Table 3.8.4, every approved NDA had subjects whose ocular inflammation was cleared by week 1 (days 7-8), but was not cleared at week 2 (days 14-15) post-surgery. The percentage of these subjects in the phase 3 studies combined ranged from 3% to 8%. At week 2 post-surgery, the majority of these subjects had cell counts in the range of 1-5 cells, some had cell counts in the ranger of 6-15, and few had cell counts >16, or >30, or >50. How these patients were handled in the primary endpoint efficacy analyses is addressed in Section 3.8.5.

Table 3.8. 4: **Number of subjects whose ocular inflammation was cleared by week 1 (days 7-8) but was not cleared at week 2 (days 14-15) post-surgery in the 7 approved NDAs**

Definition of "cleared inflammation" /NDA (# of subjects in all Phase 3 studies combined)	**# of subjects with cleared inflammation at Week 1 post-surgery**	**Cell counts at Week 2 post-surgery**					
		0 cell	**1-5 cells**	**6-15 cells**	**16-30 cells**	**> 30 cells**	**> 50 cells**
"0 cell & no flare"							
Current NDA203168 (440)	15 (3.4%)	0	13	2	0	0	0
NDA021664 Bromday (575)	24 (4.2%)	1	16	5	1	0	1
NDA021664 Xibrom (527)	19 (3.6%)	11	5	3	0	0	0
NDA203491 Ilevro (1870)	146 (7.8%)	7	111	20	7	1	0
NDA021862 Nevanac (590)	21 (3.6%)	1	17	3	0	0	0
NDA200738 Lotemax Ointment (805)	33 (4.1%)	10	18	3	2	0	0
"0 cell"							
NDA202872 Lotemax Gel (813)	31 (3.8%)	0	27	3	0	1	0
NDA022212 Durezol (220)*	9 (4.1%)	0	9	0	0	0	0

*Based on the subjects who were treated with Durezol BID or QID, as the submitted datasets didn't include the vehicle-treated subjects.

3.8.4 Varied time points and analyses were used for the primary endpoint of cleared ocular inflammation

The primary endpoint of cleared ocular inflammation was evaluated at 1 week (days 7-8) or 2 weeks (days 14-15) post surgery. Specifically, as shown in Table 3.8.5, the primary endpoint of cleared ocular inflammation was evaluated at three different visit time points: Day 8 in 3 NDAs (Lotemax ointment, Lotemax gel, and Durezol), or Day 14 in 2 NDAs (Nevanac and Ilevro), or Day 15 in 2 NDAs (Xibrom and Bromday). This information indicates that treatment effects on ocular inflammation at both time points, days 7-8 and days 14-15, are clinically relevant and important for prescribing physicians and patients to understand the treatment effects of an approved drug.

This review conducted/replicated the analysis results using the original data and the agreed/recommended endpoints at both time points (days 7-8 and days 14-15) for all these NDAs except the Durezol NDA for which only partial data were located (vehicle data were not located). The analysis results confirmed the original reviewers' conclusions that all these NDAs provided substantial statistical evidence of efficacy for the treatment of ocular inflammation for the test products. However, the protocol-defined primary efficacy analysis results in the current NDA and in the Bromday NDA are not consistent with those in the other NDAs. For each of the 7 approved NDAs and the current NDA, Table 3.8.4 shows that there were about 3% to 8% subjects in the phase 3 studies whose ocular inflammation was cleared by week 1 (days 7-8), but was not cleared at week 2 (days 14-15) post-surgery. The current NDA and the Bromday NDA treated subjects whose ocular inflammation was cleared at or prior to day 8, but was not cleared at day 15 as successes "by day 15", whereas the other NDAs that reported this time point treated those subjects as failures.

Table 3.8. 5: Timing of Primary Endpoint in 7 Approved NDAs

NDA	Days of Evaluation	Day of primary endpoint	Analysis of primary endpoint
Current NDA203168 NDA021664 Bromday	1, 3, 8, 15, 22	Day 15	Cleared at Day 15 or if not cleared at Day 15 but cleared at or prior to Day 8
NDA021664 Xibrom	1, 3, 8, 15, 22, 29	Day 15	Cleared at Day 15 (otherwise counted as failures)
NDA202872 Lotemax NDA200738 Lotemax	1, 3, 8, 15, 18	Day 8	Cleared at Day 8
NDA203491 Ilevro NDA021862 Nevanac	1, 3, 7, 14	Day 14	Cleared at Day 14 (otherwise counted as failure)
NDA022212 Durezol	1, 3, 8, 15, 29	Day 8	Cleared at Day 8 (cleared rates at Day 15 are also included in the labeling)

3.8.5 Varied information on the efficacy endpoint and results for ocular inflammation were included in labeling

As summarized in Table 3.8.6, there are differences in whether or how the information on the definition of the efficacy endpoint and the efficacy results for ocular inflammation was included in labeling.

Three package inserts provide a clear quantitative definition for the ocular inflammation endpoint:

- "Complete clearing (a cell count of 0)" for Durezol
- "Complete resolution of anterior chamber cells (cell count of 0)" for Lotemax gel
- "Complete resolution of anterior chamber cells and flare (cell count of 0 and no flare)" for Lotemax ointment

Four package inserts provide no clear quantitative definition for the ocular inflammation endpoint:

- "Reduction of ocular inflammation (to trace inflammation or clearing)" for Xibrom
- "Measurable signs of inflammation (cell and flare)" for Nevanac
- "Clearing of ocular inflammation" for Bromday
- "Resolution of inflammation" for Ilevro

The efficacy results of the treatment effect on ocular inflammation presented in labeling varies:

- No data for Nevanac and some data (point estimates by treatment group with or without confidence interval for treatment difference) for other applications
- Point estimates by treatment group without confidence interval for treatment difference
  - Xibrom, Durezol, Bromday, Lotemax ointment, and Lotemax gel
- Point estimates by treatment group with confidence interval for treatment difference
  - Ilevro
- Results presented for only one time point
  - Xibrom (Day 15), Bromday (Day 15), Ilevro (Day 14), Lotemax ointment (Day 8), and Lotemax gel (Day 8)
- Results presented for two time points
  - Durezol (Day 8 and Day 15)
- Results presented based on pooled study data
  - Durezol

Finally, although not reviewed in any detail, it is noted that the "pain-free" information presented in labeling varies anywhere from Day 1 up to Day 15.

Table 3.8. 6: Information of Ocular Inflammation Presented in Labeling for 7 Approved NDAs

NDA	Definition of Ocular Inflammation Endpoint	Efficacy Results
Proposal for current NDA203168	Same as for Bromday	Same as for Bromday
NDA021664 Bromday	No clear definition; with wordings "clearing of ocular inflammation".	Point estimates at Day 15: 46-47% vs. 25-29%
NDA021664 Xibrom	No clear definition; with wordings "reduction of ocular inflammation (to trace inflammation or clearing).	Point estimates: 62-66% vs. 40-48%
NDA202872 Lotemax	Complete resolution of anterior chamber cells (cell count of 0).	Point estimates at Day 8: 31% vs. 14-16%
NDA200738 Lotemax	Complete resolution of anterior chamber cells and flare (cell count of 0 and no flare).	Point estimates at Day 8: 24-32% vs. 11-14%
NDA203491 Ilevro	No clear definition; with wordings "resolution of inflammation".	Count and percentage of subjects with resolution of inflammation at Day 14 are presented in a table; the treatment difference (plus 95% CI) in resolution rates at Day 14 is also presented.
NDA021862 Nevanac	No clear definition; but with wordings: "measurable signs of inflammation (cell and flare)"	No rates included in labeling
NDA022212 Durezol	Complete clearing to (a cell count of 0).	Based on pooled study data: counts and percentage of subjects with ocular clearance are presented for Day 8 and Day 15 in a table; a p-value < 0.01 for comparing Durezol with vehicle is indicated for both Day 8 and Day 15.

4 Recommendations for the Clinical Studies Section of the Labeling for the Current NDA203168 Prolensa

The following is the Clinical Studies section of the applicant's proposed labeling (dated 06/06/2012) for the current NDA:

(b) (4)

[redacted] (b) (4)

This proposal is similar to the approved drug labeling for Bromday in NDA021664. The proposed labeling states that [redacted] (b) (4)

However, as discussed in Section 2, the applicant' efficacy results for this endpoint counted 15 subjects whose ocular inflammation was not cleared (with cell counts in the range of 1-15 cells) at Day 15 as successes by Day 15. The statistical reviewer's analysis treated those subjects as failures. Though the Bromday NDA used the same analysis as in the current NDA, the other 6 NDAs reported analyses more in line with the statistical reviewer's analysis which we believe is clearer for prescribing physicians and patients. The analysis results from the current NDA and the Bromday NDA could be problematic, as shown in Section 3.4, where subjects who had cell counts >16 cells or > 50 cells at Day 15 were counted as success.

Furthermore, the statistical reviewer's analysis is also consistent with Dr. Wiley Chambers' opinion written in his review for the Xibrom NDA: "*Evaluation of clearance in these studies however, was not true clearance because evaluations demonstrating 1-5 cells per high power field (normally called trace inflammation) were counted as cleared.*" The statistical reviewer's analysis also addresses the concern raised by the medical reviewer for the Xibrom NDA that rebound is a common occurrence; the endpoint as defined in the current NDA and the Bromday NDA does not address this concern or the sustainability of the effect of clearing ocular inflammation at the end of the 14-day active-treatment period.

To ensure clarity of the study efficacy results in the drug labeling, the team leader recommends presenting the primary statistical reviewer's efficacy results for the endpoint of cleared ocular inflammation in the Clinical Studies section of the final drug labeling. For the Clinical Studies section of the labeling for the current NDA, the statistical team has the following general recommendations:

Bromfenac 0.07% QD for the treatment of postoperative inflammation and reduction of ocular pain was evaluated in two multi-center, randomized, double-masked, parallel-group and vehicle (placebo)-controlled studies. Patients undergoing cataract surgery self-administered bromfenac 0.07% or vehicle once daily, beginning 1 day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. Complete clearance of ocular inflammation (0 cell and no flare) was assessed at Days 1, 3, 8 and 15 post-surgery using slit lamp biomicroscopy. The pain score was self-reported. In the intent-to-treat analysis, bromfenac 0.07% was superior to vehicle as shown in the following table.

Study	Visit	Proportion of Subjects with Cleared Ocular Inflammation (0 cell and no flare)		
		Bromfenac 0.07% QD	**Vehicle QD**	**Difference (%) (Asymptotic 95% CI)**
Study 1	Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6 (8.4, 26.8)
	Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5 (21.4, 43.8)
Study 2	Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3 (6.7, 27.9)
	Day 15	50/ 110 (45.4%)	30/ 110 (27.3%)	18.2 (5.7, 30.7)
		Proportion of Subjects Who Were Pain Free		
Study 1	Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 (25.9, 49.6)
Study 2	Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9 (8.7, 33.1)

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/s/

YAN WANG
04/04/2013

TSAE YUN D LIN
04/04/2013
I concur.

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/BLA #:	NDA203168
Drug Name:	Bromfenac 0.07% Ophthalmic Solution
Indication(s):	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Applicant:	Bausch+Lomb
Date(s):	Stamp date: June 6, 2012
	PDUFA date: April 7, 2013
Review Priority:	Standard (Addendum to the Primary Statistical Review)
Biometrics Division:	DBIV
Statistical Reviewer:	Abel Tilahun Eshete
Concurring Reviewers:	Yan Wang
Medical Division:	Ophthalmology
Clinical Team:	Medical Reviewer: William Boyd, M.D.
Project Manager:	Michael Puglisi

Keywords: anterior chamber cells, anterior chamber flare**,** summed ocular inflammation score (SOIS), ocular pain, cataract surgery.

This is an addendum for the statistical review dated 03/04/2013. The purpose of this addendum is to provide edits and clarification on the reported p-values in the primary statistical review and the corresponding drug labeling recommendation provided in the review (see DARRTS entry on 03/04/2013).

The statistical review team for this NDA provided recommendations for the clinical section of the drug labeling. (b) (4) [redacted] the statistical review team's recommended labeling presents results both for Day 8 and 15.

A secondary review by the Statistical team leader showed that, there were three NDAs (Lotemax and Durezol) with a similar indication where Day 8 was the day at which the primary efficacy endpoint was evaluated. We therefore believe that the inclusion of results for Day 8 will make it easier for prescribing physicians to have a clearer understanding of the time effect of this product.

As noted in the original review, the bromfenac 0.07% ophthalmic solution treatment group and the placebo group were compared using the Fisher's exact test. Confidence intervals for the treatment differences were computed using the normal approximation method. Both the applicant and the statistical reviewer used the Hochberg's method to adjust multiple comparisons using the same efficacy outcome at different time points.

The analysis results for the proportion of subjects with cleared ocular inflammation by the applicant and the statistical reviewer are presented in Table 2 and Table 1.

Both analyses confirmed that, compared to the placebo group, the bromfenac 0.07% group had a significantly higher proportion of subjects with cleared ocular inflammation by Day 15. Additionally, both analyses confirmed that compared to the placebo group, the bromfenac 0.07% group had a significantly higher proportion of subjects with cleared ocular inflammation by Day 8. Note that only p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity using the Hochberg's method in both analyses. The unadjusted and adjusted p-values based on the Hochberg method are presented in Table 1 and Table 2.

Table 1: FDA Reviewer's Results for the Proportion of Subjects with Cleared Ocular Inflammation

Visit	S00124-ER				
	Bromfenac 0.07% N=112	**Placebo N=108**	**% difference (Asymptotic 95% CI)**	**Unadjusted P-value**	**Adjusted P-value[1]**
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979	0.4979

Day 3	6 (5.4%)	1 (0.9%)	4.4 %(-0.1%, 9.0%)	0.1194	0.2388
Day 8	27 (24.1%)	7 (6.5%)	17.6% (8.4%, 26.8%)	0.0003	0.0009*
Day 15 (Primary Endpoint)	51(45.5%)	14 (13.0%)	32.5% (21.4%, 43.8%)	<0.0001	<0.0001
Day 22	63 (56.2%)	33 (30.6%)	25.7% (13.0%, 38.3%)	0.0001	0.0006*
	S00124-WR				
Visit	**Bromfenac 0.07% N=110**	**Placebo N=110**	**% difference (Asymptotic 95% CI)**	**Unadjusted P-value**	**Adjusted P-values [1]**
Day 1	3 (2.7%)	4 (3.6%)	1.8% (-0.6%, 4.4%)	>0.9999	>0.9999
Day 3	7 (6.4%)	6 (5.4%)	0.91 %(-5.3%, 7.1%)	>0.9999	>0.9999
Day 8	33 (30.0%)	14 (12.7%)	17.3% (6.7%, 27.9%)	0.0028	0.0084*
Day 15 (Primary Endpoint)	50 (45.4%)	30 (27.3%)	18.2% (5.7%, 30.7%)	0.0076	0.0076
Day 22	67 (60.9%)	40 (36.4%)	24.5% (11.7%, 37.3%)	0.0004	0.0017*

[1]The p-values are from the Fisher's exact test and treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity using the Hochberg method. * P-values changed from the original review.

Table 2: Applicant's Results for the Proportion of Subjects with Cleared Ocular Inflammation

	S00124-ER				
Visit	**Bromfenac 0.07% N=112**	**Placebo N=108**	**% difference (Asymptotic 95% CI)**	**Unadjusted P-value**	**Adjusted P-value**
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979	0.4979
Day 3	7 (6.3%)	1 (0.9%)	5.3 %(0.5%, 10.2%)	0.0657	0.1314
Day 8	30 (26.8%)	8 (7.4%)	19.4% (9.8%, 28.9%)	<0.0001	0.0006
Day 15 (Primary Endpoint)	54 (48.2%)	18 (16.7%)	31.5% (19.9%, 43.2%)	<0.0001	<0.0001
Day 22	74 (66.1%)	57 (52.8%)	13.3% (0.4%, 26.2%)	0.0545	0.1314
	S00124-WR				
Visit	**Bromfenac 0.07% N=110**	**Placebo N=110**	**% difference (Asymptotic 95% CI)**	**Unadjusted P-value**	**Adjusted P-value[1]**
Day 1	3 (2.7%)	4 (3.6%)	-0.91% (-5.5%, 3.7%)	>0.9999	>0.9999
Day 3	8 (7.3%)	7 (6.4%)	0.91 %(-5.7%, 7.6%)	>0.9999	>0.9999
Day 8	36 (32.7%)	18 (16.4%)	16.4% (5.2%, 27.5%)	0.0074	0.0370
Day 15 (Primary Endpoint)	54 (49.1%)	35 (31.8%)	17.3% (4.5%, 30.0%)	0.0132	0.0132
Day 22	81 (73.6%)	63 (57.3%)	16.4% (4.0%, 28.7%)	0.0157	0.0470

[1]The p-values are from the Fisher's exact test and treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity using the Hochberg method.

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/s/

ABEL T ESHETE
04/01/2013

YAN WANG
04/01/2013
I concur.

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/BLA #:	NDA203168
Drug Name:	Bromfenac 0.07% Ophthalmic Solution
Indication(s):	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Applicant:	Bausch+Lomb
Date(s):	Stamp date: June 6, 2012
	PDUFA date: April 7, 2013
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Abel Tilahun Eshete
Concurring Reviewers:	Yan Wang
Medical Division:	Ophthalmology
Clinical Team:	Medical Reviewer: William Boyd, M.D.
Project Manager:	Michael Puglisi

Keywords: anterior chamber cells, anterior chamber flare**,** summed ocular inflammation score (SOIS), ocular pain, cataract surgery.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This NDA seeks approval for a lower dose (modified) formulation of bromfenac 0.07% QD for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

The efficacy and safety data from two Phase 3 studies, S00124-WR and S00124-ER, were included in this NDA. The two studies shared a common protocol and a statistical analysis plan. Both studies were double-masked, placebo-controlled, and randomized (with a 1:1 ratio) studies conducted in the United States, with S00124-WR including study sites in the west region and S00124-ER in the east region.

A total of 220 subjects were randomized in each study. The primary efficacy endpoint was the proportion of subjects with cleared ocular inflammation by Day 15, which was defined as the summed ocular inflammation score (SOIS) of Grade 0 (0 cells and absence of flare) at any post surgery visit prior to and including Day 15. The key secondary efficacy endpoint was the proportion of subjects who were pain free at Day 1.

The primary efficacy analysis was conducted on the ITT population, defined as all randomized subjects. The Fisher's exact test was used to compare the bromfenac 0.07% and the placebo groups with respect to the primary efficacy endpoint and the key secondary endpoint. Missing data were imputed using the Last Observation Carried Forward (LOCF) method.

The primary analysis results for the primary endpoint and the key secondary endpoint are presented in Table 1 and Table 2. Compared to the placebo group, the bromfenac 0.07% group had a significantly higher proportion of subjects with cleared ocular inflammation by Day 15, defined as no cells and no flare, and a significantly higher proportion of subjects who were pain free at Day 1.

In both studies, compared to the treatment group, the placebo group had a much higher percentage of subjects who received a rescue therapy. The applicant considered subjects who received a rescue therapy as having missing data and a "failure" was imputed for all subjects except for one subject in S00124-WR study. Additionally, there were 15 subjects, who were treated as successes in the applicant's primary efficacy analysis despite a non-zero score at Day 15. The summed ocular inflammation and mean anterior chamber cells score for each of these subjects for each visit is presented in the appendix in Table 55 and Table 56 respectively. The reviewer believes that the primary efficacy analysis should treat every subject who received a rescue therapy or did not have cleared ocular inflammation at Day 15 as a failure.

The results from the reviewer's analysis in which subjects who received a rescue therapy or did not have cleared ocular inflammation at Day 15 set as failures are presented in Table 3. Compared to the applicant's analysis, this analysis lowered the percentage of subjects with cleared ocular inflammation by approximately 3% in both treatment groups. Thus, the treatment differences were comparable with the results from the applicant's analysis, demonstrating statistically significant efficacy of the test product.

To examine the robustness of the primary efficacy analysis results with respect to the methods of handling missing data, both the applicant and the statistical reviewer conducted sensitivity analyses using various methods of handling missing data. The sensitivity analyses included Observed Case analysis (OC), Baseline Observation Carried Forward (BOCF), multiple imputations and setting missing values as failures.

The important difference between the applicant's and the reviewer's sensitivity analyses was that, unlike the applicant's analysis, subjects who received a rescue therapy were not considered as having missing data, instead, these subjects were always treated as failures in the reviewer's analyses. As a result, only 21(9.5%) and 32(14.5%) subjects were considered as having missing data for the primary efficacy endpoint in S00124-ER and S00124-WR studies respectively. The reviewer's sensitivity analyses yielded similar results as the primary analysis (Table 4).

The reviewer also summarized the proportion of subjects who achieved a zero cell score at Day 15. Among the subjects who achieved a zero cell score at Day 15, all subjects except one subject in the S00124-ER study also achieved zero flare scores. Thus the percentage of subjects who had zero cell score and the percentage of subjects who had clear ocular inflammation (zero cell score and zero flare score) is the same in each treatment group except in the placebo group for the S00124-ER study.

With respect to safety, both studies showed that there was no significant safety concern. The safety population in the two studies combined consisted of 416 subjects (212 subjects in the bromfenac 0.07% and 204 subjects in the placebo group). No deaths were reported in either study. The most commonly reported adverse event was eye pain. In terms of severity, only a small percentage (1.4% in bromfenac group and 2% in the placebo group) of the study population reported serious adverse events.

Table 1: Applicant's Results for the Primary and Key Secondary Endpoints (S00124-ER)

Percentage of Subjects with Cleared Ocular Inflammation				
Visit	**Bromfenac 0.07% N=112**	**Placebo N=108**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979
Day 3	7 (6.3%)	1 (0.9%)	5.3 %(0.5%, 10.2%)	0.1314
Day 8	30 (26.8%)	8 (7.4%)	19.4% (9.8%, 28.9%)	0.0006
Day 15 (Primary Endpoint)	54 (48.2%)	18 (16.7%)	31.5% (19.9%, 43.2%)	<0.0001
Day 22	74 (66.1%)	57 (52.8%)	13.3% (0.4%, 26.2%)	0.1314
Percentage of Subjects Who Were Pain Free				
Day 1 (Secondary	91 (81.3%)	47 (43.5%)	37.7 %(25.9%, 49.6%)	<0.0001

Endpoint)				
Day 3	97 (86.6%)	57 (52.8%)	33.8 %(22.5%, 45.2%)	<0.0001
Day 8	105 (93.8%)	64 (59.3%)	34.5% (24.2%, 44.8%)	<0.0001
Day 15	104 (92.9%)	73 (67.6%)	25.3% (15.2%, 35.3%)	<0.0001

Source: Table 8 and 22 of the applicant's study reports (CI was calculated by the reviewer using normal approximation)

Table 2: Applicant's Results for the Primary and Key Secondary Endpoints (S00124-WR)

Percentage of Subjects with Cleared Ocular Inflammation				
Visit	**Bromfenac 0.07% N=110**	**Placebo N=110**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	3 (2.7%)	4 (3.6%)	-0.91% (-5.5%, 3.7%)	>0.9999
Day 3	8 (7.3%)	7 (6.4%)	0.91 %(-5.7%, 7.6%)	>0.9999
Day 8	36 (32.7%)	18 (16.4%)	16.4% (5.2%, 27.5%)	0.0370
Day 15 (Primary Endpoint)	54 (49.1%)	35 (31.8%)	17.3% (4.5%, 30.0%)	0.0132
Day 22	81 (73.6%)	63 (57.3%)	16.4% (4.0%, 28.7%)	0.0470
Percentage of Subjects Who Were Pain Free				
Day 1 (Secondary Endpoint)	84 (76.4%)	61 (55.5%)	20.9% (8.7%, 33.1%)	0.0017
Day 3	95 (86.4%)	58 (52.7%)	33.6 %(22.3%, 45.0%)	<0.0001
Day 8	99 (90.0%)	68 (61.8%)	28.2% (17.5%, 38.9%)	<0.0001
Day 15	100 (90.9%)	74 (67.3%)	23.6% (13.3%, 33.9%)	<0.0001

Source: Table 8 and 22 of the applicant's study reports (CI was calculated by the reviewer using normal approximation)

Table 3: FDA Reviewer's Results for the Percentage of Subjects with Cleared Ocular Inflammation by Visit

Visit	**S00124-ER**			
	Bromfenac 0.07% N=112	**Placebo N=108**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979
Day 3	6 (5.4%)	1 (0.9%)	4.4 %(-0.1%, 9.0%)	0.2388
Day 8	27 (24.1%)	7 (6.5%)	17.6% (8.4%, 26.8%)	0.0004
Day 15 (Primary Endpoint)	51(45.5%)	14 (13.0%)	32.5% (21.4%, 43.8%)	<0.0001

Day 22	63 (56.2%)	33 (30.6%)	25.7% (13.0%, 38.3%)	<0.0001
S00124-WR				
Visit	**Bromfenac 0.07% N=110**	**Placebo N=110**	**% difference (Asymptotic 95% CI)**	**P-value**
Day 1	3 (2.7%)	4 (3.6%)	1.8% (-0.6%, 4.4%)	>0.9999
Day 3	7 (6.4%)	6 (5.4%)	0.91 %(-5.3%, 7.1%)	>0.9999
Day 8	33 (30.0%)	14 (12.7%)	17.3% (6.7%, 27.9%)	0.0112
Day 15 (Primary Endpoint)	50 (45.4%)	30 (27.3%)	18.2% (5.7%, 30.7%)	0.0076
Day 22	67 (60.9%)	40 (36.4%)	24.5% (11.7%, 37.3%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 4: FDA Reviewer's Sensitivity Analysis Results for the Primary Efficacy Endpoint (S00124-ER)

Method	Bromfenac 0.07% N=112	Placebo N=108	% Difference (95% CI)	P-value
LOCF	54 (48.2%)	18 (16.7%)	31.5% (19.9%, 43.2%)	<0.0001
OC	47(46.1%)	17(17.2%)	28.9% (16.7%, 41.1%)	<0.0001
BOCF	57 (50.9%)	26(24.1%)	26.8% (14.5%, 39.1%)	<0.0001
Multiple Imputations	56 (50.4%)	24(22.7%)	27.7% (15.4%, 39.9%)	<0.0001
All Missing Subjects set as Failures	47 (42.0%)	17 (15.7%)	26.2% (14.9%, 37.6%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

Table 5: FDA Reviewer's Sensitivity Analysis Results for the Primary Efficacy Endpoint (S00124-WR)

Method	Bromfenac 0.07% N=110	Placebo N=110	% Difference (95% CI)	P-value
LOCF	54 (49.1%)	34 (30.9%)	18.2 %(5.5%, 30.9%)	0.0088
OC	51(50.5%)	32 (31.7%)	18.8% (5.5%, 32.1%)	0.0297
BOCF	60 (54.5%)	41 (37.3%)	17.3% (4.3%, 30.2%)	0.0441
Multiple Imputations	60(54.5%)	42 (37.7%)	16.8 %(3.5%, 30.0%)	0.0511
All Missing Subjects set as Failures	51(46.4%)	32 (29.1%)	17.3 %(4.7%, 30.0%)	0.0121

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

1.1 Conclusion and Recommendation

This NDA has provided substantial evidence for efficacy and safety of bromfenac 0.07% QD for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. This reviewer recommends the approval of this NDA. The reviewer also recommends that the language below and the efficacy results in Table 6 be presented in the "Clinical Studies" section of the final labeling.

The safety and efficacy of bromfenac 0.07% QD for the treatment of postoperative inflammation and reduction of ocular pain was established in 2 multi-center, randomized, double-masked, parallel-group and placebo-controlled studies. Patients undergoing cataract surgery self-administered bromfenac 0.07% or placebo once daily, beginning 1 day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. Complete clearance of ocular inflammation (0 cells and no flare) was assessed at Days 1, 3, 8 and 15 post-surgery using slit lamp biomicroscope. The pain score was self-reported. In the intent-to-treat analysis, bromfenac 0.07% was superior to placebo (Table 6).

Table 6: Summary Results for Labeling

		Cleared Ocular Inflammation		
Study	**Visit**	**Bromfenac 0.07%**	**Placebo**	**Difference (Asymptotic 95% CI)**
Study 1	Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6% (8.4%, 26.8%)
	Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5% (21.4%, 43.8%)
Study 2	Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3% (6.7%, 27.9%)
	Day 15	50/ 110 (45.4%)	30/ 110 (27.3%)	18.2% (5.7%, 30.7%)
			Pain Free	
Study 1	Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 % (25.9%, 49.6%)
Study 2	Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9% (8.7%, 33.1%)

2 INTRODUCTION

This NDA included data from two phase 3 studies (S00124-ER and S00124-WR) to support the safety and efficacy of bromfenac 0.07% ophthalmic solution in the treatment of ocular inflammation and pain associated with cataract surgery. The two pivotal studies submitted by the applicant shared a common protocol and statistical analysis plan. These two studies were the main focuses of this review.

2.1 Overview

This section provides a brief overview of the class and indication of the studied drug, the history of the drug development and outlines the specific studies reviewed.

2.1.1 Drug Class and Indication

Bromfenac belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs), which work by blocking the production of prostaglandins, mediators of various kinds of systemic and localized (i.e., ocular) inflammation. Bromfenac blocks prostaglandin production by inhibiting cyclooxygenase (COX), the enzyme that converts arachidonic acid to cyclic endoperoxides, precursors of prostaglandins. Bromfenac was developed by [redacted (b) (4)] with the goal of achieving anti-inflammatory, antipyretic, and analgesic effects greater than other commercially available NSAIDs. Bromfenac has been shown to be an extremely potent inhibitor of COX and subsequent prostaglandin synthesis.

2.1.2 History of Drug Development

Bronuck® (bromfenac sodium ophthalmic solution) 0.1% was approved in Japan in July 2000, and it is indicated for the treatment of blepharitis, conjunctivitis, scleritis (including episcleritis) and post operative inflammation. The formulation of bromfenac that was approved for use in Japan is identical to that approved for use in the US. Xibrom® (bromfenac ophthalmic solution) 0.09%, dosed BID, was approved by the Food and Drug Administration (FDA) in March 2005 for the treatment of post-operative ocular inflammation and in January 2006 for the treatment of post operative ocular pain. Bromday™ (bromfenac ophthalmic solution) 0.09% dosed once daily (QD), was approved by the FDA in October 2010 for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.

The applicant argued that successful development of bromfenac ophthalmic solution 0.09% BID and 0.09% QD, as well as studies conducted with bromfenac ophthalmic solution [redacted (b) (4)] showing similar safety and efficacy results suggested that lower concentration of bromfenac ophthalmic solution would also show clinical efficacy. The sponsor is thus now requesting the approval of a lower dose (modified) formulation of the same drug (bromfenac 0.07% QD) for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

The sponsor had requested two Special Protocol Assessments (SPA) and both were rejected by the agency. On January 21, 2011, the applicant requested a SPA for a Phase 3 clinical protocol titled: Efficacy and Safety of Bromfenac Ophthalmic Solution vs. Placebo for the Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery. The request was denied on February 7, 2011 because the Agency believed that the protocol did not specify the final formulation of the drug product to be studied; information the agency deemed critical to an assessment of the protocol. The applicant submitted another SPA together with a revised protocol on February 28, 2011. Based on the information submitted in the revised protocol; the agency determined that the design and planned analysis of the study did not adequately address the objectives necessary to support a regulatory submission. The agency also provided responses to the applicant's questions and communicated five additional comments to the applicant. Two of the five comments were statistical comments. One of the statistical comments recommended the applicant to construct a 95% confidence interval for the treatment differences and the second one recommended that sensitivity analyses be conducted using different approaches for handling missing values (such as baseline value carried forward and multiple imputations) in order to evaluate the robustness of study results based on the proposed LOCF method.

On April 28, 2011, the applicant submitted a final protocol and a statistical analysis plan (SAP) for Study S00124, titled "Efficacy and Safety of Bromfenac Ophthalmic Solution vs. Placebo for the Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery". After a review of this protocol, a statistical comment requesting an additional sensitivity analysis using the multiple imputation method was communicated with the sponsor.

In a pre-NDA teleconference on 29 August 2011, the FDA stated that the performed clinical pharmacokinetic studies were adequate to support the filing of bromfenac ophthalmic solution 0.07% and no additional clinical pharmacokinetic studies are needed. No additional pharmacological studies were conducted for this NDA.

2.1.3 Studies Reviewed

Two studies (S00124-ER and S00124-WR), both phase 3, multi-center, randomized, double-masked, parallel group and placebo controlled are used to support the NDA application for bromfenac 0.07% Ophthalmic Solution for Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery. The brief summaries of these studies are given in Table 7. The two studies shared a common protocol and statistical analysis plan. In both studies subjects were randomly allocated to either bromfenac 0.07% Ophthalmic Solution or a placebo. In study S00124-WR, a total of 220 subjects from 19 sites (out of 24 initiated sites), all within the United States, were involved. The sites were located in 8 states (CA, OR, AZ, MO, OK, CO, ID and KS). Similarly, in study S00124-ER a total of 220 subjects from 20 sites (out of 28 initiated sites) all within the United States were involved. The sites were located in 11 states (TX, IN, MD, OH, AR, FL, MI, KY, IL, PA and NY).

Table 7: Summary of Pivotal Studies Reviewed

Study ID	Number of Study Centers (Locations)	Study Start Enrollment Status, Date, Enrollment Goal / Total Enrollment	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	Sex M/F Mean Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
S00124 -ER	20	05 May 2011 (first subject enrolled) to 21 July 2011 (last subject completed) 200 planned / 220 randomized	Phase 3, multi-center, double-masked, randomized, parallel-group, placebo-controlled	bromfenac Ophthalmic Solution 0.07% QD vs. placebo QD	efficacy and safety	bromfenac 0.07%: 112/109 placebo: 108/102	16 days of study drug dosing	81 M/ 139 F 67.4 yrs (39-87 yrs)	Male or female, at least 18 years of age, scheduled for unilateral cataract surgery	cleared ocular inflammation (SOIS of 0) *by* Day 15
S00124 -WR	19	05 May 2011 (first subject enrolled) to 29 July 2011 (last subject completed) 200 planned/ 220 randomized	Phase 3, multi-center, double-masked, randomized, parallel-group, placebo-controlled	bromfenac Ophthalmic Solution 0.07% QD vs. placebo QD	efficacy and safety	bromfenac 0.07%: 110/104 placebo: 110/100	16 days of study drug dosing	72 M/ 148 F 69.5 yrs (18-93 yrs)	Male or female, at least 18 years of age, scheduled for unilateral cataract surgery	cleared ocular inflammation (SOIS of 0) *by* Day 15

Source: Table 4 of the ISE.

2.2 Data Sources

The data sources for this review included the applicant's clinical study reports for both studies and the integrated safety and efficacy analysis reports. Additionally, the applicant submitted SAS datasets electronically. Both SDTM and ADAM data formats were used. The data sets are located at \\Cdsesub1\evsprod\NDA203168\0000. The analysis programs are located at \\Cdsesub1\evsprod\NDA203168\0003. The updated subgroup analysis results are located at \\Cdsesub1\evsprod\NDA203168\0004 and the updated summary tables for subject dispositions and the corresponding SAS programs are located at \\Cdsesub1\evsprod\NDA203168\0005.

3 STATISTICAL EVALUATION

This section provides a detailed review of the two pivotal studies.

3.1 Data and Analysis Quality

The submitted data are generally of good quality. The applicant submitted data using the standard STDM and ADAM formation. They however did not include analysis programs for some of their analysis until they were requested. Case report forms were included for few subjects. The final statistical analysis plan and the amended protocols are all submitted. There was no need to get support from the Computational Science Center to conduct the analysis and reproduce the results of the applicant.

3.2 Evaluation of Efficacy

This section summarizes the design of the two studies and the corresponding efficacy results submitted by the applicant and the reviewers own analysis.

3.2.1 Study Design and Endpoints

The two studies considered in this review shared a common protocol and a statistical analysis plan. Both are phase 3, multi-center, randomized, double-masked, parallel group and placebo controlled studies designed to investigate the safety and efficacy of bromfenac 0.07% ophthalmic solution in the treatment of ocular inflammation and pain associated with cataract surgery.

In each study, 220 subjects who signed the informed consent and met the inclusion/exclusion criteria were randomized to receive either bromfenac ophthalmic solution 0.07% QD or placebo using a computer generated randomization code. In S00124-ER, 112 subjects were randomized to receive bromfenac and 108 were randomized to placebo, while for study S00124-WR, 110 subjects each were randomized to the bromfenac and placebo groups.

The subjects, investigators and ISTA staff were masked to treatment group assignment for the duration of the study. Masking was only broken if specific emergency treatment

was required and un-masking would aid in the treatment of the subject. Individual subject assignments were kept secure and confidential by ISTA's Director of Quality Assurance and Compliance.

Subjects were screened between 1 and 8 days prior to the initiation of dosing with bromfenac 0.07%. Subjects were evaluated on Days 1, 3±1, 8±1, 15±1 following cataract surgery. In addition, subjects had a follow-up visit on Day 22 (+3) following surgery or 7 days (+3) after their last dose of the bromfenac 0.07% if the subject prematurely discontinued the bromfenac 0.07%.

The primary objective was to investigate the efficacy of a lower dose/modified formulation of bromfenac QD for the treatment of ocular inflammation associated with cataract surgery in subjects who have undergone cataract extraction with posterior chamber intraocular lens (PCIOL) implantation. The primary efficacy endpoint was the proportion of subjects with cleared ocular inflammation by Day 15, which was defined as the summed ocular inflammation score (SOIS) of Grade 0 (0 cells and absence of flare) at any post-surgery visit prior to and including Day 15. The reviewer believes that, the applicant's definition of the primary endpoint allows for subjects who relapse after achieving a zero score in earlier visits to be counted as success. In the primary efficacy analysis, subjects who have a non-zero score at Day 15 should be treated as failures even if they had a zero score at earlier visits.

The summed ocular inflammation score was computed as the sum of the mean anterior chamber cells score and anterior flare score. The mean anterior chamber cell score was the average grade of two cell counts. The cell counts were graded as 0, 0.5, 1, 2, 3 and 4 corresponding to 0, 1-5, 6-15, 16-25, 26-50 and greater than 50 cell counts respectively. The flare was graded using a 5 point scale as 0, 1, 2, 3, 4 corresponding to Complete absence, Very slight (barely detectable), Moderate (iris and lens hazy) and Intense (fibrin clot) respectively. The two grades were then added together to get the SOIS score, based on which the primary efficacy endpoint was derived.

The secondary objective was to investigate the efficacy of a lower dose/modified formulation of bromfenac 0.07% for the treatment of ocular pain associated with cataract surgery in subjects who have undergone cataract extraction with PCIOL implantation. The main secondary efficacy outcome was the proportion of subjects that were pain free (i.e., pain grading of "None" on the ocular comfort grading assessment ((OCGA) at Day 1. Additionally, proportions of subjects with Grade 0 for SOIS by each visit (Days 1, 3, 8 and 22) and mean values for the SOIS, anterior chamber cells, anterior chamber flare, and pain, at each visit were considered for analysis.

3.2.2 Methodologies

The bromfenac 0.07% ophthalmic solution treatment group and the placebo group were compared with respect to the primary efficacy outcome using the Fisher's exact test. Confidence intervals for the treatment differences were computed using the normal approximation method. For the secondary and safety outcomes, Chi-square for

dichotomous or non-ordered categorical response measures and t-test or Wilcoxon Rank Sum test for continuous variables and ordered categorical response measures were employed. The Hochberg's method was used to adjust multiple comparisons using the same efficacy outcome at different time points.

The applicant anticipated two types of missing values. The first was from subjects who were not responding to Investigative Product (IP) and who have required alternative medical management (i.e., rescue therapy), and second was from subjects who missed scheduled evaluations but continued on IP treatment during the study. However since a rescue therapy was required because of a treatment failure; subjects who received a rescue therapy should be treated as failures in the analyses. The reviewer's analysis sets subjects who received a rescue therapy as failures and only consider subjects who missed scheduled evaluations but continued on IP treatment during the study as missing. Note that, although only two types of missing values were anticipated, in reality, other types of missing values might occur. For example, subjects who discontinued IP prematurely and did not receive any rescue therapy but had missed visits or subjects who are lost-to-follow-up would be treated as missing.

All analyses of efficacy were conducted on the ITT population, defined as all randomized subjects that were analyzed in the group to which they were randomized. For the primary analysis, the Last Observation Carried Forward (LOCF) approach was used as a main tool to impute missing values. In the applicant's analysis, for subjects who received a rescue medication prior to Day 15, the observed outcome nearest (on or before) the date of receiving rescue medication was carried forward and used in the determination of the missing outcome. For subjects who missed scheduled evaluations, the outcome from the last visit at which it was measured was carried forward.

The Observed Case analysis (OC), Baseline Observation Carried Forward (BOCF) and multiple imputation approaches were used as sensitivity analyses to investigate the robustness of the primary efficacy analysis. The observed case analysis ignores all subjects who had missing values, whereas the BOCF is similar to the LOCF except that the baseline score was used to impute missing values. An additional analysis in which all subjects with missing values for the primary efficacy outcome set as failures was also conducted. For the multiple imputations, the applicant followed a two step approach. In the first step a single imputation using the Markov chain Monte Carlo (MCMC) method was used to create a monotone missing pattern. In the second step, a regression approach in which the outcome at a particular visit used as a response, and site and all outcomes prior to that visit used as covariates was applied. After the imputation, the SOIS grade was created by setting SOIS scores less than 0.5 as zero and one otherwise. For each imputed data, a logistic regression model with treatment indicator as a covariate was fitted. The proportion of subjects with SOSI score of zero was then determined using the parameter estimates from the logistic regression model. The P-value for the difference in proportions was computed using the Wald's Chi-square test.

The reviewer's multiple imputation approach was based on the multivariate normal approximation in which all measurements from a given subjects were used to impute

missing outcomes. This approach involves drawing from a multivariate normal distribution of all the variables in the imputation model using the Markov chain Monte Carlo (MCMC) method. This approach does not require the missing pattern to be monotone. Once the imputation had been completed, the primary outcome was created by dichotomizing the resulting SOIS score as above and below zero. The proportion of subjects with SOSI grade of zero from each imputed data was summarized and was then compared using the Fisher's exact test.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Demographic and Baseline Characteristics

There were no baseline imbalances between the bromfenac 0.07% QD group and the placebo group in the demographics of age, gender, race or study eye iris color. The mean age of participants in study S00124-WR was slightly higher than those in study S00124-ER. In both studies, there were more female participants than male participants; and the majority of participants were white. The percentage of participants with brown eyes was higher than other colored eyes (Table 8).

Table 8: Demographic Profile of Subjects

Parameter		S00124-ER		S00124-WR		Pooled Data	
		0.07% QD	Placebo QD	0.07% QD	Placebo QD	0.07% QD	Placebo QD
ITT Population	(N)	112	108	110	110	222	218
Age (years)							
	Mean (SD)	67.2 (10.52)	67.6 (10.07)	69.6 (10.79)	69.4 (9.24)	68.4 (10.70)	68.5 (9.68)
	Min, Max	39 – 87	40 - 85	18 - 93	46 - 90	18 - 93	40 – 90
Gender							
Male	n (%)	41 (36.6%)	40 (37.0%)	40 (36.4%)	32 (29.1%)	81 (36.5%)	72 (33.0%)
Female	n (%)	71 (63.4%)	68 (63.0%)	70 (63.6%)	78 (70.9%)	141 (63.5%)	146 (67.0%)
Race							
American Indian or Alaska Native	n (%)	0	0	1 (0.9%)	0	1 (0.5%)	0
Asian	n (%)	0	1 (0.9%)	4 (3.6%)	7 (6.4%)	4 (1.8%)	8 (3.7%)
Black or African American	n (%)	13 (11.6%)	8 (7.4%)	9 (8.2%)	9 (8.2%)	22 (9.9%)	17 (7.8%)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0	0	0	0
White	n (%)	88 (78.6%)	91 (84.3%)	79 (71.8%)	71 (64.5%)	167 (75.2%)	162 (74.3%)
Other	n (%)	11 (9.8%)	8 (7.4%)	17 (15.5%)	23 (20.9%)	28 (12.6%)	31 (14.2%)
Iris Color (Study Eye)							
Black	n (%)	0	0	0	0	0	0
Blue	n (%)	28 (25.0%)	36 (33.3%)	29 (26.4%)	29 (26.4%)	57 (25.7%)	65 (29.8%)
Brown	n (%)	57 (50.9%)	39 (36.1%)	52 (47.3%)	54 (49.1%)	109 (49.1%)	93 (42.7%)

Gray	n (%)	0	4 (3.7%)	1 (0.9%)	1 (0.9%)	1 (0.5%)	5 (2.3%)
Green	n (%)	8 (7.1%)	12 (11.1%)	16 (14.5%)	9 (8.2%)	24 (10.8%)	21 (9.6%)
Hazel	n (%)	19 (17.0%)	17 (15.7%)	12 (10.9%)	16 (14.5%)	31 (14.0%)	33 (15.1%)
Other	n (%)	0	0	0	1 (0.9%)	0	1 (0.5%)

Source: Table 6 of ISE.

3.2.3.2 Patient Disposition

For both studies, the percentage of subjects who completed the study was comparable between bromfenac 0.07% QD and the placebo group. Note that, a subject was considered to have completed the study if the subject took all study drug and completed all study visits **or** discontinued IP prematurely and completed the final study visit (7-day follow up assessment). The inclusion of subjects who discontinued IP prematurely and completed the final study visit as completers might have inflated the reported percentage of study completers.

The percentage of patients in the bromfenac 0.07%, who discontinued IP prematurely was lower than those in the placebo group (9.8% vs. 43.5%) and (20.9% vs. 44.5%) for study S00124-ER and study S00124-WR respectively. For study S00124-ER, among the patients who discontinued IP prematurely, 36.4% and 76.6% in bromfenac 0.07% QD and the placebo group respectively had received a rescue therapy. The corresponding percentages for study S00124-WR were 34.8% and 67.3%. For both studies, there was no significant difference in the percentage of subjects who discontinued the study early (Table 9 and Table 10). This result should however be interpreted in relation to the way study completion was defined.

Table 9: Summary of Subject Dispositions (S00124-ER)

	Bromfenac 0.07% QD n (%)	**Placebo QD n (%)**
Number of Subject Randomized	112	108
Subjects who Completed the Study	109 (97.3%)	102 (94.4%)
Subjects Discontinue IP Prematurely	11 (9.8%)	47 (43.5%)
Subjects who Received any Rescue Therapy*	4 (36.4%)	36 (76.6%)
Subjects who Received Rescue Therapy for pain and inflammation (Eye)	4 (36.4%)	36 (76.6%)
Subjects who Discontinued the Study Early	3 (2.7%)	6 (5.6%)
Primary Reason for Early Termination:		
Withdrawal of Consent/Non-Compliance	2 (1.8%)	3 (2.8%)
Lost to Follow-Up	0	0
Death	0	0
Other	1 (0.9%)	3 (2.8%)
Cancelled Surgery	0	1

Enrollment Not Met	1	1
Visit Schedule	0	1

Source: Separately submitted patient disposition tables by the applicant
* Subjects who received a rescue therapy among those who discontinued IP

Table 10: Summary of Subject Dispositions (S00124-WR)

	Bromfenac 0.07% QD n (%)	**Placebo QD n (%)**
Number of Subject Randomized	110	110
Subjects who Completed the Study	104 (94.5%)	100 (90.9%)
Subjects Discontinue IP Prematurely	23 (20.9%)	49 (44.5%)
Subjects who Received any Rescue Therapy*	8 (34.8%)	33 (67.3%)
Subjects who Received Rescue Therapy for pain and inflammation (Eye)	8 (34.8%)	33 (67.3%)
Subjects who Discontinued the Study Early	6 (5.5%)	10 (9.1%)
Primary Reason for Early Termination:		
Withdrawal of Consent/Non-Compliance	4 (3.6%)	3 (2.7%)
Lost to Follow-Up	0	0
Death	0	0
Other	2 (1.8%)	7 (6.4%)
Cancelled Surgery	2	2
Disallowed Medication at Enrollment	0	1
Disallowed Medication During Study	0	1
Experienced SAE	0	2
Inappropriate Randomization	0	1

Source: Separately submitted patient disposition tables by the applicant
* Subjects who received a rescue therapy among those who discontinued IP

The proportion of subjects who completed a given visit is presented in Table 11 and Table 12. A subject was considered to have completed a visit if at least one procedure was performed during the visit. From the tables, we can see that, in both studies, there were more subjects who didn't complete visits in the placebo group compared to the bromfenac 0.07% group. In the treatment group there were more subjects who didn't complete a visit in study S00124-WR than S00124-ER. Note that the increase in the proportion of completed visit at Day 22 was because subjects were expected to report for a 7-day follow up assessment at Day 22 regardless of the reason they left the study early.

Table 11: Percentage of Subjects who Completed Study Visits (S00124-ER)

Number (%) of Subjects Completing	**Bromfenac 0.07% N = 112**	**Placebo N = 108**
Day 1	108 (96.4%)	102 (94.4%)
Day 3	105 (93.8%)	101 (93.5%)

Day 8	100 (89.3%)	72 (66.7%)
Day 15	100 (89.3%)	59 (54.6%)
Day 22	109 (97.3%)	102 (94.4%)

Source: Table 5 of the applicant's study report

Table 12: Percentage of Subjects who Completed Study Visits (S00124-WR)

	Bromfenac 0.07% N = 110	**Placebo N = 110**
Day 1	102 (92.7%)	99 (90.0%)
Day 3	99 (90.0%)	96 (87.3%)
Day 8	93 (84.5%)	83 (75.5%)
Day 15	87(79.1%)	60 (54.5%)
Day 22	104 (94.5%)	100 (90.9%)

Source: Table 5 of the applicant's study report

Table 13 provides summary of reasons for missing data for the primary efficacy endpoint. The applicant treated subjects who received a rescue therapy as missing. As a result, they reported a total of 12 (10.9%) and 49(44.5%) subjects with missing data in the treatment and placebo groups respectively for S00124-ER study. The corresponding figures for S00124-WR study were 23 (20.5%) and 50(46.3%) in the treatment and placebo groups respectively. In the reviewer's analysis, subjects who received a rescue therapy were treated as failure. As a consequence, for S00124-ER study, only 8(8.2%) and 13 (10.9%) subjects had missing values for the primary efficacy endpoint in the treatment and the placebo group respectively. The corresponding figures for S00124-WR study were 15(13.4%) and 17 (15.7%) respectively.

Table 13: Summary of Reasons for Missing Data

Reasons	**Study S00124-ER**		**Study S00124-WR**	
	Bromfenac 0.07% N = 110	**placebo N = 110**	**Bromfenac 0.07% N = 112**	**placebo N = 108**
Required Rescue Therapy	4 (3.6%)	36 (32.7%)	8(7.1%)	33 (30.5%)
Other Reasons	8 (8.2%)	13 (10.9%)	15(13.4%)	17 (15.7%)

Source: Reviewer's analysis.

3.2.4 Results and Conclusions

The sections below provide a detailed summary of the efficacy results and conclusions provided by the applicant and the reviewer's analysis for each study.

3.2.4.1 Efficacy Results for S00124-ER study

The SOIS score was computed as the sum of the mean anterior chamber cells score and anterior flare score. Figure 1 displays the histogram of the SOIS score by Day 15. The SOIS score was highly skewed for the bromfenac 0.07% group, with the largest proportion of subjects having lower SOIS scores compared to the placebo group. The

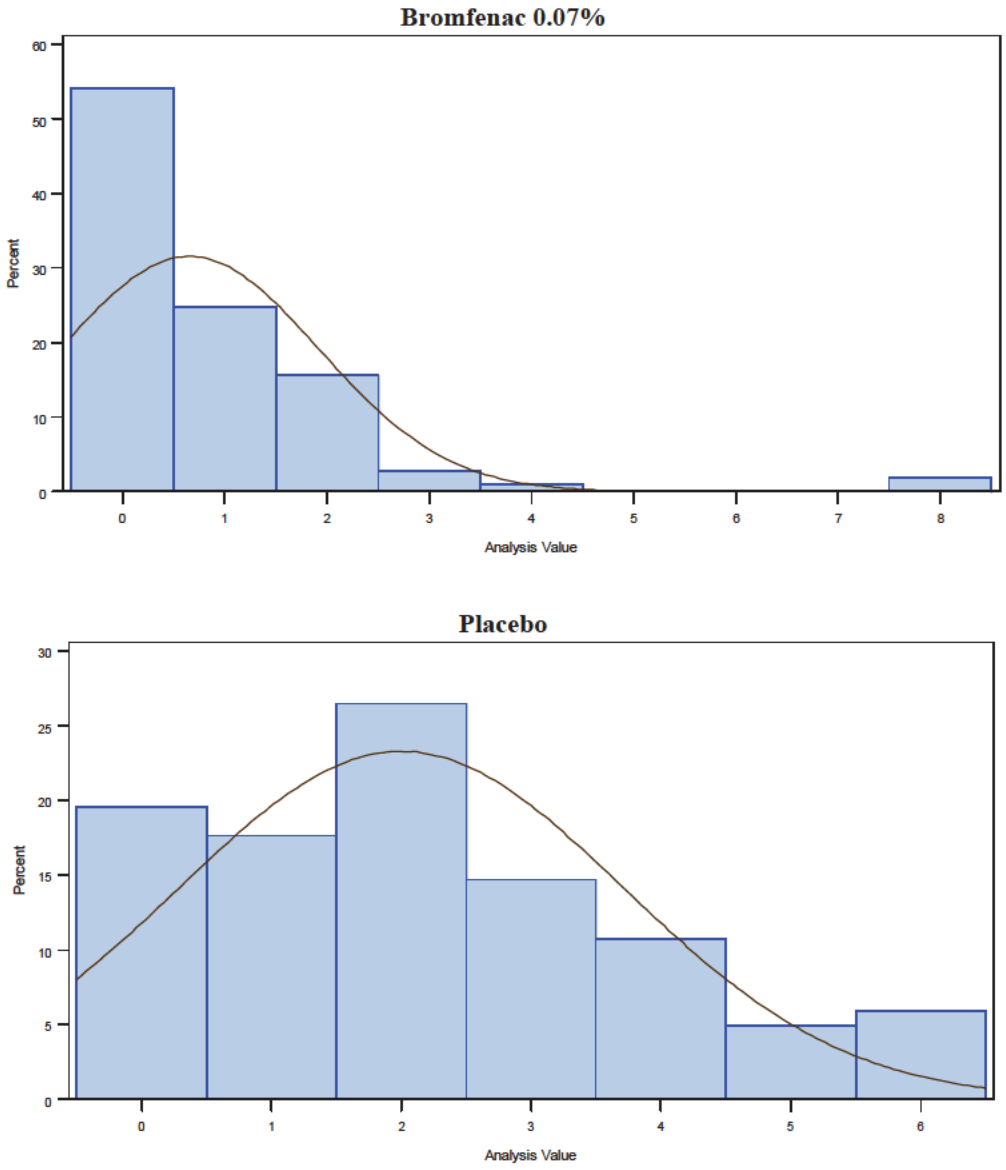
descriptive summaries of the SOIS score by Day 15 are displayed in Table 14. The bromfenac group had a significantly lower mean SOIS score and was slightly less variable compared to the placebo group.

Table 14: Descriptive Summary of SOIS Score by Day 15 (S00124-ER)

Measure	Bromfenac 0.07% N= 112	Placebo N = 108	Mean difference (95% CI)
Mean	0.70	2.0	-1.3(-1.7, -0.9)
Median	0.25	1.25	
Minimum, Maximum	0, 8.0	0, 6.0	
Standard Deviation	1.3	1.7	

Source: Reviewer's analysis

Figure 1: Histogram of SOIS Score by Day 15 (S00124-ER)



Based on the applicant's analysis results, the bromfenac 0.07% group had a significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 15 compared with the placebo group (48.2%, vs. 16.7%; p<0.0001). There was no significant difference in the proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 1, Day 3 and Day 22. There was however significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) in the bromfenac 0.07% group compared with the placebo group by Day 8 (26.8% vs. 7.4%; p=0.0006; Table 15).

Table 15: Applicant's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	% difference (Asymptotic 95% CI)	P-value
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979
Day 3	7 (6.3%)	1 (0.9%)	5.3 %(0.5%, 10.2%)	0.1314
Day 8	30 (26.8%)	8 (7.4%)	19.4% (9.8%, 28.9%)	0.0006
Day 15 (Primary Endpoint)	54 (48.2%)	18 (16.7%)	31.5% (19.9%, 43.2%)	<0.0001
Day 22	74 (66.1%)	57 (52.8%)	13.3% (0.4%, 26.2%)	0.1314

Source: Table 8 of the applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity.

Seven subjects with a non-zero score at day 15 but were treated as successes in the applicant's primary efficacy analysis because of a zero score they had in one of the earlier study visit days. The reviewer believes that the primary efficacy analysis should treat every subject who received a rescue therapy or didn't have cleared ocular inflammation at Day 15 as a failure. This analysis still resulted in a significant difference favoring the bromfenac 0.07% group by Day 8 and 15 (Table 16).

Table 16: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	% difference (Asymptotic 95% CI)	P-value
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.6%, 4.4%)	0.4979
Day 3	6 (5.4%)	1 (0.9%)	4.4 %(-0.1%, 9.0%)	0.2388
Day 8	27 (24.1%)	7 (6.5%)	17.6% (8.4%, 26.8%)	0.0004
Day 15 (Primary Endpoint)	51(45.5%)	14 (13.0%)	32.5% (21.4%, 43.8%)	<0.0001
Day 22	63 (56.2%)	33 (30.6%)	25.7% (13.0%, 38.3%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

The applicant conducted sensitivity analyses using the observed case, baseline carried forward and the multiple imputations approaches. In each case, subjects who received a rescue therapy were treated as missing. For the primary efficacy endpoint, the observed case analysis and the multiple imputations approaches showed significance differences favoring the bromfenac 0.07% group. There was no significance difference between the bromfenac 0.07% group and the placebo group in terms of the primary efficacy endpoint when baseline values were imputed for missing values (Table 17). The reviewer also conducted the same set of sensitivity analyses. Unlike the applicant, the reviewer treated subjects who received a rescue therapy as failures. The reviewer's analyses results were all in agreement with the results of the primary efficacy analysis.

The results of the LOCF approaches by the applicant and the reviewer were the same for both the bromfenac 0.07% and the placebo group. This was because the majority of subjects who were considered by the applicant as having "missing" values were subjects who received a rescue therapy and that the applicant's LOCF approach resulted in the imputation of "failure" for all those subjects. When all subjects with missing values were set as failures, the result was still significant in favor of the bromfenac 0.07% group (44.6% vs. 15.7%; $p<0.0001$, Table 18).

The multiple imputations results from the applicant's analysis and the one conducted by this reviewer, as expected, were slightly different. The two approaches were based on different assumptions. Additionally, the applicant used 0.5 as a cut-off point as opposed to zero for determining whether a subject was classified as success or failure. This might have increased the proportion of subjects with cleared ocular inflammation in both the treatment and the placebo groups as reflected in the higher success rate observed in applicant's multiple imputation analysis results.

The BOCF approach from the applicant's analysis showed non-significant difference, whereas the reviewer's analysis using the same approach showed a significant difference (Table 18). Given that the majority of subjects with missing measurements were subjects who received a rescue therapy and were more in the placebo group, the applicant's BOCF approach favored the placebo group because it treated subjects who received a rescue therapy as missing and imputed them as success (note: the baseline scores were zero for all randomized subjects). However, when subjects who received a rescue therapy were set as failures, as in the reviewer's sensitivity analysis, the proportion of subjects with a zero score in the placebo group was lower and hence a significance difference was observed.

Table 17: Applicant's Sensitivity Analysis for the Primary Efficacy Endpoint (S00124-ER)

Method	Bromfenac 0.07% N=112	Placebo N=108	% difference (Asymptotic 95% CI)	P-value
OC	50 (50.0%)	17 (28.8%)	21.2% (5.0%, 36.3%)	0.0495
BOCF	61(54.5%)	62 (57.4%)	-2.9% (-16.1%, 10.2%)	>0.9999
Multiple Imputations	65 (58.0%)	36 (33.3%)	24.7% (11.9%, 37.4%)	0.0027

Source: Tables 10, 12, and 13 of the applicant's study report (CI from the reviewer's analysis). Subjects who received a rescue therapy were treated as missing data.

Table 18: FDA Reviewer's Sensitivity Analysis for the Primary Efficacy Endpoint (S00124-ER)

Method	Bromfenac 0.07% N=112	Placebo N=108	% difference (Asymptotic 95% CI)	P-value
LOCF	54 (48.2%)	18 (16.7%)	31.5% (19.9%, 43.2%)	<0.0001
OC	47(46.1%)	17(17.2%)	28.9% (16.7%, 41.1%)	<0.0001
BOCF	57 (50.9%)	26(24.1%)	26.8% (14.5%, 39.1%)	<0.0001
Multiple Imputations	56 (50.4%)	24(22.7%)	27.7% (15.4%, 39.9%)	<0.0001
All missing set as failures	50 (44.6%)	17 (15.7%)	28.9% (17.4%, 40.4%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy were treated as failures.

The key secondary endpoint was the proportions of subjects who were pain free (a value of 'None' on the pain scale) at Day 1. A significantly higher proportion of subjects were pain free at Day 1 in the bromfenac 0.07% group compared with the placebo group (81.3%, 91/112 vs. 43.5%, 47/108; p<0.0001; Table 19). Similar results were also observed at Day 3 (86.6%, 97/110 vs. 52.8%, 57/108; p<0.0001), at Day 8 (93.8%, 105/112 vs. 59.3%, 64/108; p<0.0001), and at Day 15 (92.9%, 104/112 vs. 67.6%, 73/108; p<0.0001; Table 19).

Table 19: Applicant's Analysis: Percentage of Subjects Pain Free at Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	Difference (Asymptotic 95% CI)	P-value
Day 1 (Secondary Endpoint)	91 (81.3%)	47 (43.5%)	37.7 %(25.9%, 49.6%)	<0.0001
Day 3	97 (86.6%)	57 (52.8%)	33.8 %(22.5%, 45.2%)	<0.0001
Day 8	105 (93.8%)	64 (59.3%)	34.5% (24.2%, 44.8%)	<0.0001
Day 15	104 (92.9%)	73 (67.6%)	25.3% (15.2%, 35.3%)	<0.0001

Source: Table 22 of the applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons were adjusted for multiplicity.

Additional efficacy endpoints including anterior chamber cells, anterior chamber flare, and ocular pain assessments were also assessed. The results of these additional efficacy outcomes are summarized below. Similar to the primary and the key secondary outcomes, all analyses were performed on the ITT population with LOCF used as a means to impute missing values.

The proportion of subjects who had cleared cells in the bromfenac 0.07% group was significantly higher than that in the placebo group by Day 8 and by Day 15, whereas no significance differences were observed in the other days (Table 20). The proportion of subjects with Cleared Flare in the bromfenac 0.07% group was significantly higher than that in the placebo group by Day 3, Day 8 and by Day 15. No significance differences were observed in the proportion of subjects with Cleared Flare by other days (Table 21).

The mean ocular pain score was significantly lower in the bromfenac 0.07% group compared to the placebo group at Day 1, at Day 3, at Day 8 and at Day 15 visits (Table 24). The mean anterior chamber cells score for the bromfenac 0.07% group was significantly less than that for the placebo group at Day 3, at Day 8, and at Day 15 (Table 25).

Table 20 : Applicant's Analysis: Percentage of Subjects with Cleared Cells by Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	% Difference (Asymptotic 95% CI)	P-value
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.7%, 4.2%)	0.4979
Day 3	8 (7.1%)	1 (0.9%)	6.2 %(1.1%, 11.3%)	0.1066
Day 8	31 (27.7%)	9 (8.3%)	19.3% (9.6%, 29.1%)	0.0008
Day 15	54 (48.2%)	19 (17.6%)	30.6% (18.9%, 42.3%)	<0.0001
Day 22	75 (67.0%)	58 (53.7%)	13.3% (0.4%, 26.1%)	0.1072

Source: Table 14 of applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity.

Table 21: Applicant's Analysis: Percentage of Subjects with Cleared Flare by Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	% Difference (Asymptotic 95% CI)	P-value
Day 1	25 (22.3%)	15 (13.9%)	8.4% (-1.7%, 18.5%)	0.1697
Day 3	42 (37.5%)	19 (17.6%)	19.9% (8.4%, 31.4%)	0.0043
Day 8	70 (62.5%)	31 (28.7%)	33.8% (21.4%, 46.2%)	<0.0001
Day 15	87 (77.7%)	47 (43.5%)	34.2% (22.0%, 46.2%)	<0.0001
Day 22	95 (84.8%)	83 (76.9%)	8.0% (-2.4%, 18.3%)	0.1697

Source: Table 18 of applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity.

Similar to the primary efficacy endpoint, the reviewer has conducted the analysis of the Anterior chamber cell and Anterior chamber flare treating subjects who received a rescue therapy and subjects who had a non-zero score for the corresponding outcome at day 15 as failures. The results are summarized in Table 22 and Table 23. The reviewer's analysis yielded lower percentage of success rates compared to the applicant's analysis.

Table 22: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Flare by Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	Difference (Asymptotic 95% CI)	P-value
Day 1	25 (22.3%)	15 (13.9%)	8.4% (-1.7%, 18.5%)	0.1178

Day 3	39 (34.8%)	17 (15.7%)	19.1% (7.9%, 30.3%)	0.0012
Day 8	66 (58.9%)	25 (23.1%)	35.8% (23.7%, 47.9%)	<0.0001
Day 15	86 (76.8%)	38 (35.2%)	41.6% (29.7%, 53.5%)	<0.0001
Day 22	88 (78.5%)	56 (51.8%)	26.7% (14.6%, 38.8%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 23: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Cells by Each Visit (S00124-ER)

Visits	Bromfenac 0.07% N=112	Placebo N=108	Difference (Asymptotic 95% CI)	P-value
Day 1	2 (1.8%)	0 (0.0%)	1.8% (-0.7%, 4.2%)	0.4979
Day 3	7 (6.2%)	1 (0.9%)	5.3 %(0.5%, 10.2%)	0.1314
Day 8	28 (25.0%)	8 (7.4%)	17.6% (8.2%, 27.1%)	<0.0001
Day 15	51 (45.5%)	15 (13.9%)	31.6% (20.3%, 42.3%)	<0.0001
Day 22	65 (58.0%)	34 (31.5%)	26.5% (13.9%, 39.2%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 24: Applicant's Analysis: Descriptive Summary of Ocular Pain Score at Each Visit (S00124-ER)

Visits	Bromfenac 0.07% Mean (SD)	Placebo Mean (SD)	Mean Difference (Asymptotic 95% CI)	P-value
Day 1	0.2 (0.43)	0.7 (0.79)	-0.5(-0.71, -0.29)	<0.0001
Day 3	0.1 (0.35)	0.6 (0.81)	-0.5(-0.70, -0.30)	<0.0001
Day 8	0.0 (0.19)	0.5 (0.79)	-0.5(-0.68, -0.31)	<0.0001
Day 15	0.0 (0.21)	0.4 (0.69)	-0.4 (-0.58, -0.22)	<0.0001

Source: Table 24 of applicant's study report (CI from the reviewer's analysis). The p-values for treatment comparisons were adjusted for multiplicity.

Table 25: Applicant's Analysis: Descriptive Summary of Anterior Chamber Cells Score (S00124-ER)

Visits	Bromfenac 0.07% Mean (SD)	Placebo Mean (SD)	Mean Difference (Asymptotic 95% CI)	P-value
Day 1	1.2 (0.71)	1.2 (0.62)	0.0 (-0.21, 0.22)	0.6735
Day 3	0.8 (0.66)	1.2 (0.82)	-0.4 (-0.62,-0.17)	0.0006
Day 8	0.6 (0.66)	1.1 (0.84)	-0.5 (-0.72, -0.27)	<0.0001
Day 15	0.4 (0.61)	1.0 (0.88)	-0.6 (-0.82, -0.37)	<0.0001
Day 22	0.2(0.41)	0.3(0.31	-0.1 (-0.26, 0.06)	0.6735

Source: Table 15 of applicant's study report (CI from the reviewer's analysis). The p-values for treatment comparisons were adjusted for multiplicity.

Table 26: Summary of Anterior Chamber Flare Score at Each Visit (S00124-ER)

Visits	Bromfenac 0.07% Mean (SD)	Placebo Mean (SD)	Mean Difference (Asymptotic 95% CI)	P-value
Day 1	1.0 (0.75)	1.0 (0.65)	0.00 (-0.22, 0.22)	0.2979
Day 3	0.8 (0.75)	1.3 (0.83)	-0.50 (-0.73, -0.26)	<0.0001
Day 8	0.5 (0.74)	1.19 (0.88)	-0.69 (-0.92, -0.45)	<0.0001
Day 15	0.3 (0.70)	1.0 (0.95)	-0.70 (-0.94, -0.46)	<0.0001
Day 22	0.2 (0.37)	0.2(0.46)	0.00 (-0.17, 0.17)	0.2979

Source: Table 19 of study report (CI from the reviewer's analysis). The p-values for treatment comparisons were adjusted for multiplicity.

In conclusion, for this study, both the primary and the secondary objectives were met. The sensitivity analyses results also confirmed the result of the primary efficacy analysis.

3.2.4.2 Efficacy Results for S00124-WR Study

Figure 2: Histogram of SOIS Score by Day 15 (S00124-WR) displays the histogram of the SOIS score by Day 15. The SOIS score was highly skewed both for the bromfenac 0.07% and the placebo groups, with the largest proportion of subjects having lower SOIS scores in the bromfenac 0.07% group compared to the placebo group. The bromfenac group had a significantly lower mean SOIS score and was slightly less variable compared to the placebo group (Table 27).

Table 27: Descriptive Summary of SOIS Score by Day 15 (S00124-WR)

Measure	Bromfenac 0.07% N= 112	Placebo N = 108	Mean difference (95% CI)
Mean	0.70	1.68	-0.97(-1.4, -0.6)
Median	0.25	1.25	
Maximum	6.0	7.0	
Standard Deviation	1.1	1.7	

Source: From the reviewer's analysis

The applicant's primary efficacy analysis showed that the bromfenac 0.07% group had a significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 15 compared with the placebo group (49.1%, vs. 31.8%; p=0.0132). There was no significant difference in the proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 1 and Day 3. There was however significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) in the bromfenac 0.07% group compared with the placebo group by Day 8 (32.7% vs. 16.4%; p=0.0370) and by Day 22 (73.6% vs. 57.3%; p=0.0470; Table 28).

Table 28: Applicant's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit (S00124-WR)

Visits	Bromfenac 0.07% N=110	Placebo N=110	Difference (Asymptotic 95% CI)	P-value
Day 1	3 (2.7%)	4 (3.6%)	-0.91% (-5.5%, 3.7%)	>0.9999
Day 3	8 (7.3%)	7 (6.4%)	0.91 %(-5.7%, 7.6%)	>0.9999
Day 8	36 (32.7%)	18 (16.4%)	16.4% (5.2%, 27.5%)	0.0370
Day 15 (Primary Endpoint)	54 (49.1%)	35 (31.8%)	17.3% (4.5%, 30.0%)	0.0132
Day 22	81 (73.6%)	63 (57.3%)	16.4% (4.0%, 28.7%)	0.0470

Source: Table 8 of the applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity.

The reviewer repeated the primary efficacy analysis by treating every subject who received a rescue therapy or didn't have cleared ocular inflammation at Day 15 as a failure. This analysis still resulted in a significant difference favoring the bromfenac 0.07% group by Day 8 and 15 (Table 29).

Table 29: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit (S00124-WR)

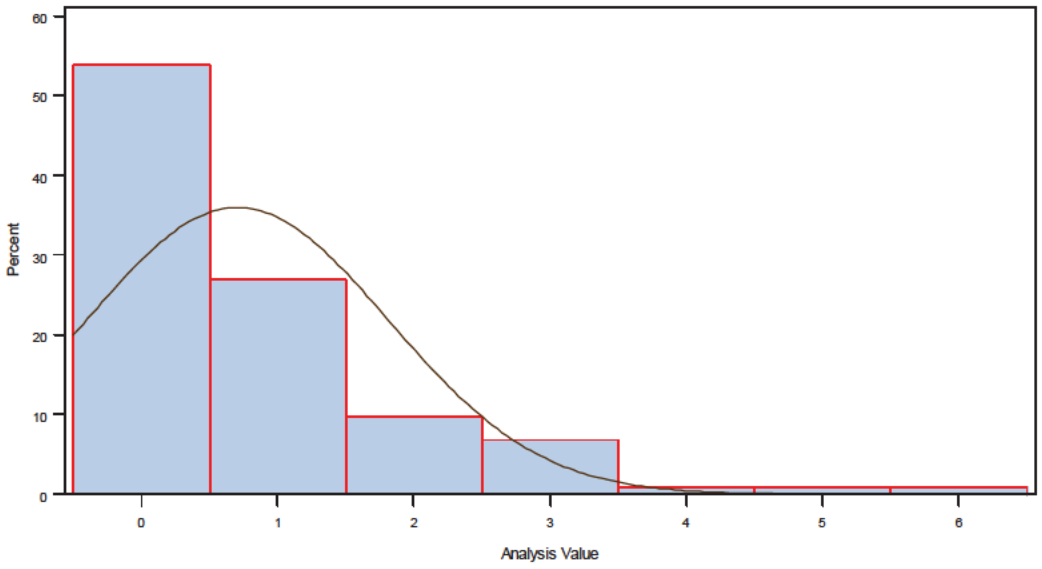
Visits	Bromfenac 0.07% N=112	Placebo N=108	% difference (Asymptotic 95% CI)	P-value
Day 1	3 (2.7%)	4 (3.6%)	1.8% (-0.6%, 4.4%)	>0.9999
Day 3	7 (6.4%)	6 (5.4%)	0.91 %(-5.3%, 7.1%)	>0.9999
Day 8	33 (30.0%)	14 (12.7%)	17.3% (6.7%, 27.9%)	0.0112
Day 15 (Primary Endpoint)	50 (45.4%)	30 (27.3%)	18.2% (5.7%, 30.7%)	0.0076
Day 22	67 (60.9%)	40 (36.4%)	24.5% (11.7%, 37.3%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

None of the applicant's sensitivity analysis results showed a significant difference between the bromfenac 0.07% group and the placebo group for the primary efficacy endpoint (Table 30). In this study, there were 23 and 49 subjects who received some type of rescue therapy in the bromfenac 0.07% and the placebo group respectively. Similarly, here also, assuming that subjects took a rescue therapy because their drug was failing, sensitivity analyses with these subjects set as failures and methods to deal with missing data applied to the other set of subjects with missing values were performed. The result of the reviewer's multiple imputations analysis showed lower proportions of subjects with cleared ocular inflammation in both the bromfenac 0.07% group and the placebo group compared to the multiple imputations results by the applicant. The conclusions from both however were the same. The reviewer's analysis results using the OC and BOCF approaches showed a significant treatment difference favoring the bromfenac 0.07%

group (Table 31). When all subjects with missing values by Day 15 were set as failures, the result was still significant in favor of the bromfenac 0.07% group (46.4% vs. 29.1%; p=0.0121; Table 31).

Figure 2: Histogram of SOIS Score by Day 15 (S00124-WR)
Bromfenac 0.07%



Placebo

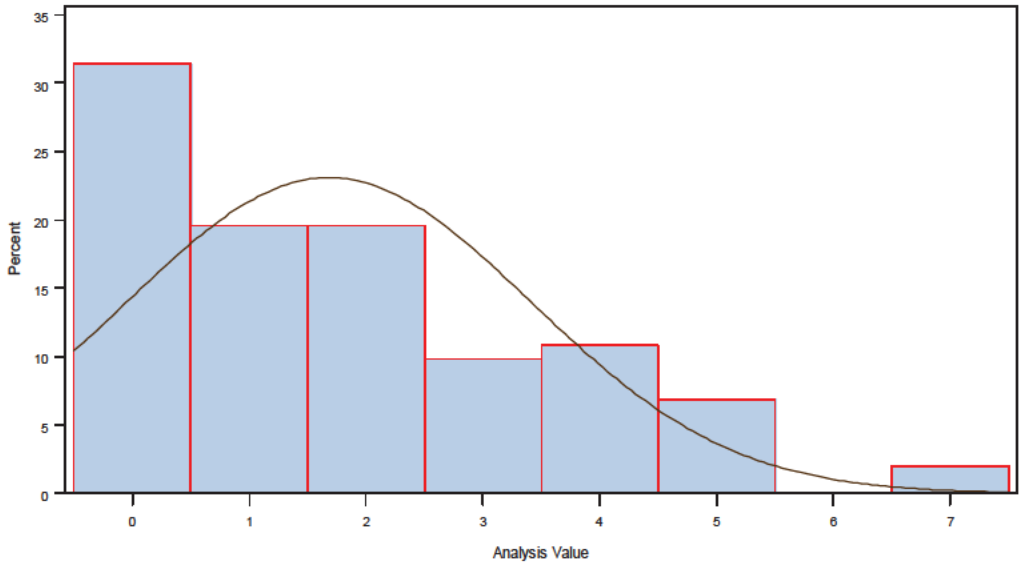


Table 30: Applicant's Sensitivity Analysis for the Primary Efficacy Endpoint (S00124-WR)

Method	Bromfenac 0.07% N=110	Placebo N=110	% Difference (Asymptotic 95% CI)	P-value
OC	51 (58.6%)	32 (53.3%)	5.3% (-11.0%, 21.6%)	>0.9999
BOCF	68 (61.8%)	74 (67.3%)	-5.4% (-18.1%, 7.2%)	>0.9999
Multiple Imputations	62 (56.1%)	46(41.8%)	14.3 %(0.5%, 28.0%)	0.1255

Source: Tables 10, 12, and 13 of the applicant's study report (CI from the reviewer's analysis).

Table 31: FDA Reviewer's Sensitivity Analysis for the Primary Efficacy Endpoint (S00124-WR)

Method	Bromfenac 0.07% N=110	Placebo N=110	% Difference (Asymptotic 95% CI)	P-value
LOCF	54 (49.1%)	34 (30.9%)	18.2 %(5.5%, 30.9%)	0.0088
OC	51(50.5%)	32 (31.7%)	18.8% (5.5%, 32.1%)	0.0297
BOCF	60 (54.5%)	41 (37.3%)	17.3% (4.3%, 30.2%)	0.0441
Multiple Imputations	60(54.5%)	42 (37.7%)	16.8 %(3.5%, 30.0%)	0.0511
All missing set as failures	51(46.4%)	32 (29.1%)	17.3 %(4.7%, 30.0%)	0.0121

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

A significantly higher proportion of subjects were pain free at Day 1 in the bromfenac 0.07% group compared with the placebo group (76.4%, 84/110 vs. 55.5%, 61/110; p=0.0017; Table 19). Similar results were also observed at Day 3 (86.4%, 95/110 vs. 52.7%, 58/110; p<0.0001), at Day 8 (90.0%, 99/110 versus 61.8%, 68/110; p<0.0001), and at Day 15 (90.9%, 100/110 vs. 67.3%, 74/110; p<0.0001; Table 32).

Table 32: Applicant's Analysis: Percentage of Subjects Pain Free at Each Visit (S00124-WR)

Visits	Bromfenac 0.07% N=110	Placebo N=110	Difference (Asymptotic 95% CI)	P-value
Day 1 (Secondary Endpoint)	84 (76.4%)	61 (55.5%)	20.9% (8.7%, 33.1%)	0.0017
Day 3	95 (86.4%)	58 (52.7%)	33.6 %(22.3%, 45.0%)	<0.0001
Day 8	99 (90.0%)	68 (61.8%)	28.2% (17.5%, 38.9%)	<0.0001
Day 15	100 (90.9%)	74 (67.3%)	23.6% (13.3%, 33.9%)	<0.0001

Source: Table 22 of the applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons were adjusted for multiplicity.

The proportion of subjects who had cleared cells in the bromfenac 0.07% group was significantly higher than that in the placebo group by Day 8 and by Day 15, whereas no significance differences were observed in the other days (Table 33). The proportion of subjects with Cleared Flare in the bromfenac 0.07% group was significantly higher than

that in the placebo group by Day 8 and by Day 15. No significance differences were observed in the proportion of subjects with Cleared Flare by other days (Table 34).

The mean ocular pain score was significantly lower in the bromfenac 0.07% group compared to the placebo group at Day 1, at Day 3, at Day 8 and at Day 15 visits (Table 37). The mean anterior chamber cells score for the bromfenac 0.07% group was significantly less than that for the placebo group at Day 3, at Day 8, and at Day 15 (Table 38). The mean anterior chamber flare scores for the bromfenac 0.07% group were significantly less than that of the placebo group at Day 3, at Day 8, and at Day 15 (Table 39).

Table 33: Applicant's Analysis: Percentage of Subjects with Cleared Cells by Each Visit (S00124-WR)

Visits	Bromfenac 0.07% N=110	Placebo N=110	Difference (Asymptotic 95% CI)	P-value
Day 1	3 (2.7%)	5 (4.5%)	-1.8% (-6.7%, 3.1%)	>0.9999
Day 3	8 (7.3%)	8 (7.3%)	NA	>0.9999
Day 8	36 (32.7%)	18 (16.4%)	16.4% (5.2%, 27.5%)	0.0370
Day 15	54 (49.1%)	35 (31.8%)	17.3% (4.5%, 30.0%)	0.0528
Day 22	81 (73.6%)	64 (58.2%)	15.4% (3.1%, 27.8%)	0.0676

Source: Table 14 of the applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity.

Table 34: Applicant's Analysis: Percentage of Subjects with Cleared Flare by Each Visit (S00124-WR)

Visits	Bromfenac 0.07% N=110	Placebo N=110	Difference (Asymptotic 95% CI)	P-value
Day 1	23 (20.9%)	21 (19.1%)	1.8% (-8.7%, 12.3%)	0.8663
Day 3	55 (50.0%)	39 (35.5%)	18.2% (5.4%, 31.0%)	0.1220
Day 8	79 (71.8%)	47 (42.7%)	29.1% (16.6%, 41.6%)	0.0001
Day 15	87 (79.1%)	62 (56.4%)	22.7% (10.7%, 34.7%)	0.0020
Day 22	99 (90.0%)	90 (81.8%)	8.2% (-0.9%, 17.3%)	0.2401

Source: Table 18 of the applicant's study report (CI from the reviewer's analysis). LOCF was used to impute Missing values at each study visit. The p-values for treatment comparisons at Days 1, 3, 8, and 22 were adjusted for multiplicity.

Similar to the primary efficacy endpoint, the reviewer has also conducted the analysis of the Anterior chamber cell and Anterior chamber flare with subjects who received a rescue therapy and subjects who had a non-zero score for the corresponding outcome at day 15 set as failures. The results are summarized in Table 35 and Table 36.

Table 35: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Cells by Each Visit (S00124-WR)

Visits	Bromfenac 0.07% N=110	Placebo N=110	Difference (Asymptotic 95% CI)	P-value
Day 1	3 (2.7%)	5 (4.5%)	-1.8% (-6.7%, 3.1%)	>0.9999
Day 3	7 (6.4%)	6 (5.4%)	0.9% (-5.3%, 7.1%)	>0.9999
Day 8	33 (30.0%)	14 (12.7%)	17.2% (6.7%, 27.9%)	0.0084
Day 15	50 (45.4%)	30 (27.3%)	18.2% (5.7%, 30.7%)	0.0076
Day 22	67 (60.9%)	41 (37.3%)	23.6% (10.8%, 36.5%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 36: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Flare by Each Visit (S00124-WR)

Visits	Bromfenac 0.07% N=110	Placebo N=110	Difference (Asymptotic 95% CI)	P-value
Day 1	23 (20.9%)	21 (19.1%)	1.8% (-8.7%, 12.3%)	0.8663
Day 3	50 (45.4%)	30 (27.3%)	18.2% (5.7%, 30.7%)	0.0152
Day 8	73 (66.4%)	33 (30.0%)	36.4% (24.1%, 48.7%)	<0.0001
Day 15	81 (73.6%)	47 (42.7%)	30.9% (18.5%, 43.3%)	<0.0001
Day 22	80 (72.7%)	52 (47.3%)	25.4% (12.9%, 38.0%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 37: Applicant's Analysis: Descriptive Summary of Ocular Pain Score at Each Visit (S00124-WR)

Visits	Bromfenac 0.07% Mean (SD)	Placebo Mean (SD)	Mean Difference (Asymptotic 95% CI)	P-value
Day 1	0.2 (0.52)	0.6 (0.83)	-0.4(-0.6, -0.12)	0.0003
Day 3	0.1 (0.39)	0.6 (0.75)	-0.5(-0.7, -0.32)	<0.0001
Day 8	0.0 (0.19)	0.5 (0.82)	-0.5(-0.7, -0.34)	<0.0001
Day 15	0.0 (0.17)	0.4 (0.79)	-0.4(-0.6, -0.24)	<0.0001

Source: Table 13 of the applicant's study report (CI from the reviewer's analysis). The p-values for treatment comparisons were adjusted for multiplicity.

Table 38: Applicant's Analysis: Descriptive Summary of Anterior Chamber Cells Score (S00124-WR)

Visits	Bromfenac 0.07% Mean (SD)	Placebo Mean (SD)	Mean Difference (Asymptotic 95% CI)	P-value
Day 1	1.4 (0.79)	1.4 (0.91)	0.0(-0.23, 0.23)	0.7268

Day 3	1.0 (0.65)	1.2 (0.81)	-0.2(-0.4, -0.001)	0.1646
Day 8	0.6 (0.61)	1.1 (0.94)	-0.5(-0.72, -0.28)	<0.0001
Day 15	0.5 (0.64)	1.0 (1.02)	-0.5(-0.7, -0.3)	<0.0001

Source: Table 15 of the applicant's study report (CI from the reviewer's analysis). The p-values for treatment comparisons were adjusted for multiplicity.

Table 39: Applicant's Analysis: Descriptive Summary of Anterior Chamber Flare Score at Each Visit (S00124-WR)

Visits	Bromfenac 0.07% Mean (SD)	Placebo Mean (SD)	Mean Difference (Asymptotic 95% CI)	P-value
Day 1	1.0 (0.67)	1.0 (0.68)	0.0(-0.18, 0.18)	0.7579
Day 3	0.6 (0.63)	0.9 (0.71)	-0.3(-0.48, -0.11)	0.0054
Day 8	0.3 (0.55)	0.9 (0.79)	-0.6(-0.78, -0.41)	<0.0001
Day 15	0.3 (0.54)	0.7 (0.82)	-0.4(-0.60, -0.21)	<0.0001

Source: Table 19 of the applicant's study report (CI from the reviewer's analysis). The p-values for treatment comparisons were adjusted for multiplicity.

In conclusion, for this study, both the primary and the secondary objectives were met. The success rate in the treatment group was comparable with the success rate in the S00124-ER study, but the placebo success rate was higher in this study resulting in a less significant difference between the treatment and the placebo.

3.3 Evaluation of Safety

The safety population for the two studies combined consisted of 416 subjects; 212 in the bromfenac 0.07% group and 204 in the placebo group. A total of 99 and 177 AEs had been reported in the bromfenac 0.07% group and the placebo group respectively. Eighty-three of the 99 AEs in the bromfenac 0.07% group and 111 of 177 AEs in the placebo group were unique AEs. There was a significant difference in the proportion of subjects with any kind of AE (28.8% vs. 42.6%; p=0.0041) and in the proportion of subjects who discontinued IP due to adverse event in the bromfenac 0.07% group compared to the placebo group (10/212 4.7% vs. 28/204 13.7%; p=0.0019) (Table 40). In the bromfenac 0.07% group, 46(21.7%) subjects had adverse events that were unrelated to the treatment. The corresponding figure for the placebo group was 43 (21.1%; Table 40). In the bromfenac 0.07% group, higher proportion of patients experienced mild AEs in the study eye compared to moderate or severe AEs. In the placebo group, the proportions of subjects who experienced mild and moderate AEs were comparable and both were higher than the proportion of subjects who experienced severe AEs (Table 40).

Table 40: Summary of Adverse Events

	Bromfenac 0.07% QD n (%)	Placebo QD n (%)	Total n (%)	P value
Safety Population, N	212	204	416	
Subjects with any Adverse Event	61 (28.8%)	87 (42.6%)	148 (35.6%)	0.0041
Total Number of Reported Adverse Events	99	177	276	
Number of Unique Adverse Events	83	111	170	
Subjects with an Ocular Adverse Event	52 (24.5%)	82 (40.2%)	134 (32.2%)	0.0008
Affecting the Study Eye	48 (22.6%)	82 (40.2%)	130 (31.3%)	0.0001
Affecting the Non-Study Eye	4 (1.9%)	1 (0.5%)	5 (1.2%)	0.3724
Affecting Both Eyes	3 (1.4%)	1 (0.5%)	4 (1.0%)	0.6235
Subjects with a Systemic Adverse Event	12 (5.7%)	10 (4.9%)	22 (5.3%)	0.8279
Subjects with a Serious Adverse Event	3 (1.4%)	4 (2.0%)	7 (1.7%)	0.7195
Total Number of Serious Adverse Events	3	4	7	
Number of Unique Serious Adverse Events	3	4	7	
Subjects Discontinued IP Due to an Adverse Event	10 (4.7%)	28 (13.7%)	38 (9.1%)	0.0019
Subjects with an Adverse Event by Relationship to Investigational Product				
Not Related	46 (21.7%)	43 (21.1%)	89 (21.4%)	
Possible	12 (5.7%)	33 (16.2%)	45 (10.8%)	
Probable	2 (0.9%)	10 (4.9%)	12 (2.9%)	
Definite	1 (0.5%)	1 (0.5%)	2 (0.5%)	
Subjects with an Adverse Event by Severity				
Mild	38 (17.9%)	38 (18.6%)	76 (18.3%)	
Moderate	17 (8.0%)	35 (17.2%)	52 (12.5%)	
Severe	6 (2.8%)	14 (6.9%)	20 (4.8%)	

Source: Table 6 of ISS

Table 41: Adverse Events with Incidence ≥2.0%, Stratified by Severity

Preferred Term	Bromfenac 0.07% QD			Placebo QD		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Safety Population, N	212			204		
Subjects with an Adverse Event Affecting the Study Eye or Both Eyes	30 (14.2%)	16 (7.5%)	4 (1.9%)	37 (18.1%)	33 (16.2%)	12 (5.9%)
Chambers (anterior and posterior) and lens infections and inflammations						
Anterior chamber inflammation	4 (1.9%)	6 (2.8%)	0	6 (2.9%)	9 (4.4%)	3 (1.5%)
Choroid and vitreous structural change, deposit and degeneration						
Vitreous floaters	0	0	0	5 (2.5%)	0	0
Conjunctival infections, irritations and inflammations						
Conjunctival hyperemia	0	3 (1.4%)	0	5 (2.5%)	8 (3.9%)	2 (1.0%)

Corneal infections, oedemas and inflammations						
Corneal edema	2 (0.9%)	0	0	8 (3.9%)	2 (1.0%)	0
Iris and uveal tract infections, irritations and inflammations						
Lacrimation increased	2 (0.9%)	0	0	4 (2.0%)	2 (1.0%)	1 (0.5%)
Ocular disorders NEC						
Eye pain	7 (3.3%)	5 (2.4%)	0	9 (4.4%)	7 (3.4%)	4 (2.0%)
Ocular infections, inflammations and associated manifestations						
Ocular hyperemia	0	0	0	4 (2.0%)	2 (1.0%)	0
Ocular sensation disorders						
Foreign body sensation in eyes	6 (2.8%)	1 (0.5%)	0	6 (2.9%)	2 (1.0%)	0
Photophobia	2 (0.9%)	2 (0.9%)	0	5 (2.5%)	4 (2.0%)	2 (1.0%)
Visual disorders NEC						
Vision blurred	3 (1.4%)	1 (0.5%)	0	4 (2.0%)	0	0

Source: Table 10 of ISS

The summary of the overall incidence and frequency of AEs affecting the study-eye with Table 42). The most frequent AE affecting the study eye in the bromfenac 0.07% group was eye pain which happened in 12 (5.7%) of the patients followed by anterior chamber inflammation which affected 10 (4.7%) participants (Table 42).

Table 42: Summary of Adverse Events Affecting the Study Eye with an Incidence ≥2.0%

Preferred Term	**Bromfenac 0.07% QD Studies**	
	Bromfenac 0.07% QD N = 212 n (%)	**Placebo QD N = 204 n (%)**
Subjects Reporting an AE Affecting the Study Eye or Both Eyes	50 (23.6%)	82 (40.2%)
Chambers (anterior and posterior) and lens infections and inflammations		
Anterior chamber inflammation	10 (4.7%)	18 (8.8%)
Choroid and vitreous structural change, deposit and degeneration		
Vitreous floaters	0	5 (2.5%)
Conjunctival infections, irritations, and inflammations		
Conjunctival hyperemia	3 (1.4%)	15 (7.4%)
Corenal infections, edemas and inflammations		
Corneal edema	2 (0.9%)	10 (4.9%)
Lacrimal disorders		
Lacrimation increased	2 (0.9%)	7 (3.4%)
Ocular disorders NEC		
Eye pain	12 (5.7%)	20 (9.8%)
Ocular infections, inflammations and associated manifestations		
Eye pruritus	3 (1.4%)	4 (2.0%)
Ocular hyperemia	0	6 (2.9%)

Ocular sensation disorders		
Foreign body sensation in eyes	7 (3.3%)	8 (3.9%)
Photophobia	4 (1.9%)	11 (5.4%)
Ophthalmic function diagnostic procedures		
Intraocular pressure increased	3 (1.4%)	4 (2.0%)
Visual disorders NEC		
Vision blurred	4 (1.9%)	4 (2.0%)

Source: Table 8 ISS

The summary of the overall incidence and frequency of AEs related to the study treatment and affecting the study-eye with an incidence ≥2.0% in the bromfenac 0.07% group or placebo group are presented in Table 41. More patients in the placebo group compared to the bromfenac 0.07% group experienced AEs related to the IP (Table 43).

Table 43: Summary of Adverse Events Affecting the Study Eye and Related to IP with an Incidence ≥2.0%

Preferred Term	**Bromfenac 0.07% QD Studies**	
	Bromfenac 0.07% QD N = 212 n (%)	**Placebo QD N = 204 n (%)**
Subjects reporting an IP-related adverse event affecting the Study Eye or Both Eyes	14 (6.6%)	43 (21.1%)
Chambers (anterior and posterior) and lens infections and inflammations		
Anterior chamber inflammation	5 (2.4%)	11 (5.4%)
Conjunctival infections, irritations and inflammations		
Conjunctival hyperemia	2 (0.9%)	8 (3.9%)
Corneal infections, oedemas and inflammations		
Corneal edema	1 (0.5%)	5 (2.5%)
Lacrimal disorders		
Lacrimation increased	1 (0.5%)	5 (2.5%)
Ocular disorders NEC		
Eye pain	6 (2.8%)	16 (7.8%)
Ocular infections, inflammations and associated manifestations		
Ocular hyperaemia	0	4 (2.0%)
Ocular sensation disorders		
Foreign body sensation in eyes	0	5 (2.5%)
Photophobia	1 (0.5%)	8 (3.9%)

Source: Table 13 ISS

For the pooled data only 3(1.4%) and 4(2.0%) subjects in the bromfenac 0.07% group and the placebo groups respectively reported serious adverse events (SAE) (Table 44).

Table 44: Summary of Serious Adverse Events

Preferred Term	Bromfenac 0.07% QD Studies	
	Bromfenac 0.07% QD N = 212 n (%)	Placebo QD N = 204 n (%)
Subjects reporting a Serious Adverse Event	3 (1.4%)	4 (2.0%)
Asthenic conditions		
Asthenia	0	1 (0.5%)
Eye and ear procedural complications		
Eye operation complication	1 (0.5%)	0
Ischaemic coronary artery disorders		
Angina pectoris	1 (0.5%)	0
Myocardial infarction	0	1 (0.5%)
Lower limb fractures and dislocations		
Hip fracture	1 (0.5%)	0
Lower limb fractures and dislocations		
Deep vein thrombosis	0	1 (0.5%)
Vascular hypertensive disorders NEC		
Hypertension	0	1 (0.5%)

Source: Table 15 of ISS.

A total of 10(4.7%) subjects in the in the bromfenac 0.07% group and 28 (13.7%) subjects in the placebo group reported adverse events that led to IP discontinuation.

Table 45: Adverse Events that Led to Investigational Product Discontinuation with an Incidence ≥2.0%

Preferred Term	Bromfenac 0.07% QD Studies	
	Bromfenac 0.07% QD N = 212 n (%)	Placebo QD N = 204 n (%)
Subjects reporting an Adverse Event that Led to IP Discontinuation	10 (4.7%)	28 (13.7%)
Chambers (anterior and posterior) and lens infections and inflammations		
Anterior chamber inflammation	1 (0.5%)	13 (6.4%)
Ocular disorders NEC		
Eye pain	0	4 (2.0%)

Source: Table 18 ISS.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section efficacy and safety results for subgroups formed based on gender, Race and Age will be summarized for each study. The results are based on the reviewer's definition of the primary efficacy endpoint.

4.1 Gender Race and Age

4.1.1 Subgroup Analysis for S00124-ER Study

Logistic regression models with gender, age group or race together with treatment and their interaction included were fitted. There was no significant gender by treatment interaction (p=0.1405). Similarly the treatment by race (p=0.5467) and treatment by age group interactions (p=0.4499) were both non-significant. These results highlighted that the treatment effect was consistent in the subgroups formed by these variables. A detailed look into the reviewer's analysis results comparing the treatment and the placebo groups within each subgroup formed by race, gender and race is discussed below.

For both male female participants, the bromfenac 0.07% group had a significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 15, the primary efficacy endpoint, compared with the placebo group (Male: 46.3% vs. 10.0 p=0.0004) (Female: 45.1% vs. 14.7% ; p=0.0001). For age groups ≤70 years and >70 years, there was a significantly higher proportion of subjects with SOIS Grade 0 by Day 15 in the bromfenac 0.07% group compared with the placebo group (Table 46). The bromfenac 0.07% group had a significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 15 compared to the placebo group for Caucasians participants (44.3% vs. 9.9%; p<0.0001). The difference however was non-significant for non-Caucasians (50.0% vs. 29.4% p=0.2169) (Table 47). This can be attributed to the small number of non-Caucasians in the study.

For the key secondary endpoint, pain free at Day 1, the bromfenac 0.07% group had significantly higher proportion of subjects who were pain free by Day 1 for both male (75.6% vs. 40.0% p=0.0016) and female participants (84.5% vs. 50.0% p<0.0001) and Caucasians (80.7% vs. 41.8%; p<0.0001) but the difference was only borderline significant for non-Caucasians (83.3% vs. 52.9% p=0.0454) (Table 48 and Table 49). This again can be explained by the small sample size in this subgroup. Comparison of US versus non-US has not be conducted given all sites are located within the US.

Table 46: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit, by Gender and Age Subgroups (S00124-ER)

	0.07% QD N (%)	Placebo QD N (%)	P-value
By Gender (Male)			
ITT Population	41	40	
Day 1	0 (0.0)	0 (0.0)	NE
Day 3	1 (2.4%)	0 (0.0)	>0.9999
Day 8	8 (19.5%)	3 (7.5%)	0.1935
Day 15	19 (46.3%)	4 (10.0%)	0.0004
Day 22	23 (56.1%)	11(27.5%)	0.0131
By Gender (Female)			

ITT Population	71	68	
Day 1	2 (2.8%)	0 (0.0)	0.4966
Day 3	5 (7.0%)	1 (1.5%)	0.2092
Day 8	19 (26.8%)	4 (5.9%)	0.0011
Day 15	32 (45.1%)	10 (14.7%)	0.0001
Day 22	40 (56.3%)	22 (32.4%)	0.0062
By Age (≤70 years)			
ITT Population	64	61	
Day 1	2 (3.1%)	0 (0.0)	0.4966
Day 3	5 (7.8%)	0 (0.0)	0.0579
Day 8	18 (28.1%)	4 (6.6%)	0.0019
Day 15	32 (50.0%)	9 (14.8%)	<0.0001
Day 22	36 (56.3%)	18(29.5%)	0.0037
By Age (>70 years)			
ITT Population	48	47	
Day 1	0 (0.0)	0 (0.0)	NE
Day 3	1 (2.1%)	1 (2.1%)	>0.9999
Day 8	9 (18.8%)	3 (6.4%)	0.1202
Day 15	19 (39.6%)	5 (10.6%)	0.0180
Day 22	27 (56.3%)	15 (31.9%)	0.0231

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 47: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit, by Racial Subgroup (S00124-ER)

	0.07% QD N (%)	**Placebo QD N (%)**	**P-value**
Caucasian Subjects			
ITT Population	88	91	
Day 1	1 (1.1%)	0 (0.0)	0.4916
Day 3	4 (4.5%)	1 (1.1%)	0.2058
Day 8	21 (23.9%)	5 (5.5%)	0.0005
Day 15	39 (44.3%)	9 (9.9%)	<0.0001
Day 22	47 (53.4%)	29 (31.9%)	0.0041
Non-Caucasian Subjects			
ITT Population	24	17	
Day 1	1 (4.2%)	0 (0.0)	>0.9999
Day 3	2 (8.3%)	0 (0.0)	0.5024
Day 8	6 (25.0%)	2 (11.8%)	0.4328
Day 15	12 (50.0%)	5 (29.4%)	0.2169
Day 22	16 (66.7%)	4 (23.5%)	0.0109

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 48: FDA Reviewer's Analysis: Percentage of Subjects Pain Free *at* Each Visit, by Gender and Age Subgroups (S00124-ER)

	0.07% QD N (%)	Placebo QD N (%)	P-value
By Gender (Male)			
ITT Population	41	40	
Day 1	31 (75.6%)	16 (40.0%)	0.0016
Day 3	36 (87.8%)	23 (57.5%)	0.0027
Day 8	36 (87.8%)	23 (55.0%)	0.0013
Day 15	34 (82.9%)	23 (55.0%)	0.0084
By Gender (Female)			
ITT Population	71	68	
Day 1	60 (84.5%)	31 (45.6%)	<0.0001
Day 3	61 (85.9%)	34 (50.0%)	<0.0001
Day 8	67 (94.4%)	32 (47.1%)	<0.0001
Day 15[3]	67 (94.4%)	36 (52.9%)	<0.0001
By Age (≤70 years)			
ITT Population	64	61	
Day 1	48 (75.0%)	22 (36.1%)	<0.0001
Day 3	52 (81.3%)	30 (49.2%)	0.0002
Day 8	57 (89.1%)	29 (47.5%)	<0.0001
Day 15	56 (87.5%)	34 (55.7%)	0.0001
By Age (>70 years)			
ITT Population	48	47	
Day 1	43 (89.6%)	25 (53.2%)	<0.0001
Day 3	45 (93.8%)	27 (57.4%)	<0.0001
Day 8	46 (95.8%)	25 (53.2%)	<0.0001
Day 15	45 (93.8%)	24 (51.1%)	<0.0001

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

Table 49: FDA Reviewer's Analysis: Percentage of Subjects Pain Free *at* Each Visit, by Racial Subgroup (S00124-ER)

	0.07% QD N (%)	Placebo QD N (%)	P-value
Caucasian Subjects	88	91	
Day 1	71 (80.7%)	38 (41.8%)	<0.0001
Day 3	76 (86.4%)	46 (50.5%)	<0.0001
Day 8	81 (92.0%)	46 (50.5%)	<0.0001
Day 15	79 (89.8%)	49 (53.8%)	<0.0001
Non-Caucasian Subjects	24	17	
Day 1	20 (83.3%)	9 (52.9%)	0.0454
Day 3	21 (87.5%)	11 (64.7%)	0.1280
Day 8	22 (91.7%)	8 (47.1%)	0.0031

Day 15	22 (91.7%)	9 (52.9%)	0. 0083

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

4.1.2 Subgroup Analysis for S00124-WR Study

There was no significant gender by treatment interaction (p=0.2933). Similarly, the treatment by race (p= 0.3870) and treatment by age group interactions (p=0.9690) were both non-significant. These results highlighted that the treatment effect was consistent in the subgroups formed by these variables. A detailed look into the reviewer's analysis results comparing the treatment and the placebo groups within each subgroup formed by race, gender and race is discussed below.

For female participants, the bromfenac 0.07% group had a significantly higher proportion of subjects who had cleared ocular inflammation (SOIS Grade 0) by Day 15 compared with the placebo group (47.1 vs. 26.9%; p=0.0163). For male participants however, the difference was non-significant (42.5% vs. 28.1% p=0.2281). This might be due to the small number of male participants in this study. For both age groups (≤70 years and >70 years) and for both race groups (Caucasians and non-Caucasians), there was a non-significant difference between the bromfenac 0.07% group and the placebo group with respect to the primary efficacy endpoint (Table 50--Table 52).

For the key secondary endpoint, pain free at Day 1, the bromfenac 0.07% group had significantly higher proportion of subjects who were pain free by Day 1 for male participants (80.0% vs. 53.1% p=0.0220), female participants (74.3% vs. 55.1% p=0.0170) and Caucasians (81.0% vs. 53.5%; p=0.0004) but the difference was not significant non-Caucasians (83.3% vs. 52.9% p=0.1360) (Table 53). This again can be explained by the small sample size in these subgroups. Comparison of US versus non-US has not be conducted given all sites are located within the US.

Table 50: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit, by Gender and Age Subgroups (S00124-WR)

	0.07% QD N (%)	**Placebo QD N (%)**	**P-value**
By Gender (Male)			
ITT Population	40	32	
Day 1	1 (2.5%)	1 (3.1%)	>0.9999
Day 3	4 (10.0%)	3 (9.4%)	>0.9999
Day 8	11 (27.5%)	4 (12.5%)	0.1509
Day 15	17 (42.5%)	9 (28.1%)	0.2281
Day 22	23 (57.5%)	13 (40.6%)	>0.9999
By Gender (Female)			
ITT Population	70	78	
Day 1	2 (2.9%)	3 (3.8%)	>0.9999
Day 3	3 (4.3%)	3 (3.8%)	>0.9999

Day 8	22 (31.4%)	10 (12.8%)	0.0088
Day 15	33 (47.1%)	21 (26.9%)	0.0163
Day 22	44 (62.9%)	27 (34.6%)	0.0183
By Age (≤70 years)			
ITT Population	60	57	
Day 1	2 (3.3%)	2 (3.5%)	>0.9999
Day 3	5 (8.3%)	5 (8.8%)	>0.9999
Day 8	16 (26.7%)	7 (12.3%)	0.0636
Day 15	29 (48.3%)	15 (26.3%)	0.0215
Day 22	40 (66.7%)	18 (31.6%)	0.0002
By Age (>70 years)			
ITT Population	50	53	
Day 1	1 (2.0%)	2 (3.8%)	>0.9999
Day 3	2 (4.0%)	1 (1.9%)	0.6104
Day 8	17 (34.0%)	7 (13.2%)	0.0189
Day 15	21 (42.0%)	15 (28.3%)	0.1522
Day 22	27 (54.0%)	22 (41.5%)	0.1918

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 51: FDA Reviewer's Analysis: Percentage of Subjects with Cleared Ocular Inflammation by Each Visit, by Racial Subgroup (S00124-WR)

	0.07% QD N (%)	**Placebo QD N (%)**	**P-value**
Caucasian Subjects			
ITT Population	79	71	
Day 1	1 (1.3%)	2 (2.8%)	>0.9999
Day 3	6 (7.6%)	5 (7.0%)	>0.9999
Day 8	26 (32.9%)	13 (18.3%)	0.1846
Day 15	40 (50.6%)	26 (36.6%)	0.1004
Day 22	59 (74.7%)	40 (56.3%)	0.0982
Non-Caucasian Subjects			
ITT Population	31	39	
Day 1	2 (6.5%)	2 (5.1%)	>0.9999
Day 3	2 (6.5%)	2 (5.1%)	>0.9999
Day 8	10 (32.3%)	5 (12.8%)	0.0773
Day 15	13 (41.9%)	9 (23.1%)	0.1218
Day 22	18 (58.1%)	14 (35.9%)	0.0913

Source: Reviewer's analysis. Subjects who received a rescue therapy and subjects who achieved a zero score at earlier visits but had a non-zero score at Day 15 were set as failures.

Table 52: FDA Reviewer's Analysis: Percentage of Subjects Pain Free at Each Visit, by Gender and Age Subgroups (S00124-WR)

	0.07% QD N (%)	Placebo QD N (%)	P-value
By Gender (Male)			
ITT Population	40	32	
Day 1	32 (80.0%)	17 (53.1%)	0.0220
Day 3	35 (87.5%)	18 (56.3%)	0.0035
Day 8	35 (87.5%)	22 (68.8%)	0.0790
Day 15	33 (82.5%)	16 (50.0%)	0.0049
By Gender (Female)			
ITT Population	70	78	
Day 1	52 (74.3%)	43 (55.1%)	0.0170
Day 3	60 (85.7%)	40 (51.3%)	<0.0001
Day 8	59 (84.3%)	39 (50.0%)	<0.0001
Day 15	60 (85.7%)	40 (51.3%)	<0.0001
By Age (≤70 years)			
ITT Population	60	57	
Day 1	44 (73.3%)	29 (50.9%)	0.0139
Day 3	54 (90.0%)	32 (56.1%)	<0.0001
Day 8	55 (91.7%)	28 (49.1%)	<0.0001
Day 15	55 (91.7%)	25 (43.9%)	<0.0001
By Age (>70 years)			
ITT Population	50	53	
Day 1	40 (80.0%)	31 (58.5%)	0.0270
Day 3	41 (82.0%)	26 (49.1%)	0.0008
Day 8	39 (78.0%)	33 (62.3%)	0.0907
Day 15	38 (76.0%)	31 (58.5%)	0.0639

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

Table 53: FDA Reviewer's Analysis: Percentage of Subjects Pain Free *at* Each Visit, by Racial Subgroup (S00124-WR)

	0.07% QD N (%)	Placebo QD N (%)	P-value
Caucasian Subjects			
ITT Population	79	71	
Day 1	64 (81.0%)	38 (53.5%)	0.0004
Day 3	72 (91.1%)	38 (53.5%)	<0.0001
Day 8	69 (87.3%)	42 (59.2%)	0.0001
Day 15	69 (87.3%)	40 (56.3)	<0.0001
Non-Caucasian Subjects			
ITT Population	31	39	
Day 1	20 (64.5%)	22 (56.4%)	0.6242

Day 3	23 (74.2%)	20 (51.3%)	0.0822
Day 8	25 (80.6%)	19 (48.7%)	0.0070
Day 15	24 (77.4%)	16 (41.0%)	0.0033

Source: Reviewer's analysis. Subjects who received a rescue therapy were set as failures.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed. Comparison of US versus non-US was not conducted as all sites were located within the US.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In the applicant's analyses, subjects who received a rescue therapy were treated as missing. However, given that a rescue therapy was required because of a treatment failure, these set of subjects should be treated as failures. The reviewer's analysis treated subjects who received a rescue therapy as failures in the primary efficacy analysis.

In both studies, there were subjects with a non-zero score at day 15 but were treated as successes in the primary efficacy analysis because of a zero score they had in one of the earlier study visit days. These subjects should be treated as failures in the analysis. The reviewer's analysis treated these subjects as failures in the primary efficacy analysis.

5.2 Collective Evidence

The primary and the secondary objectives were met for the two studies considered as part of the NDA submission. The success rate in the treatment group was consistent in both studies although higher placebo success rate was observed in the S00124-WR study. The study drug has an acceptable safety profile. Compared to the placebo group, the treatment group had at least a 17% higher success rate in clearing ocular inflammation by day 15 and a 20% higher rate of resolving pain at Day1.

The results of the primary efficacy analyses were consistent in the subgroups formed based on age, gender, race and iris color. For some groups however, the placebo and the bromfenac 0.07% group did not differ significantly with respect to the primary efficacy outcome most likely because of the small sample size in these subgroups.

There were no deaths reported and the majority of the study subjects encountered mild side effects, and the largest proportion of the adverse events were unrelated to the treatment. Only 10 subjects discontinued study treatment due to adverse events in the treatment group compared to the 28 in the placebo group.

5.3 Conclusions and Recommendations

In both studies, subjects in the bromfenac 0.07% group had shown a significantly higher rate of success in clearing ocular inflammation by Day 15, and a significantly higher proportion were pain free at Day 1 compared to subjects in the placebo group. In addition, the bromfenac 0.07% group showed significantly better performances in terms of the proportions of subjects with Grade 0 for SOIS at the other measurement days (1, 3, 8 and 22). Furthermore, the mean values for the SOIS, anterior chamber cells, anterior chamber flare, and pain, at each visit were lower in the treatment group compared to the placebo group. The study drug has an acceptable safety profile with no deaths reported and the majority of subjects having only mild adverse events.

In conclusion, this NDA has provided substantial evidence for efficacy and safety of the test product. This reviewer therefore recommends approval of this NDA.

5.4 Labeling Recommendations

(b) (4)

We recommend that the definition of the primary efficacy endpoint be amended to reflect the requirement of a zero score at day 15 and the following language and summary result be used for the "Clinical Studies" section of the label:

The safety and efficacy of bromfenac 0.07% QD for the treatment of postoperative inflammation and reduction of ocular pain was established in 2 multi-center, randomized, double-masked, parallel-group and placebo-controlled studies. Patients undergoing cataract surgery self-administered bromfenac 0.07% or placebo once daily, beginning 1 day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. Complete clearance of ocular inflammation (0 cells and no flare) was assessed at Days 1, 3, 8 and 15 post-surgery using slit lamp biomicroscope. The pain score was self-reported. In the intent-to-treat analysis, bromfenac 0.07% was superior to placebo (Table 54).

Table 54: Summary Results for Labeling

		Cleared Ocular Inflammation		
Study	**Visit**	**Bromfenac 0.07%**	**Placebo**	**Difference (Asymptotic 95% CI)**

Study 1	Day 8	27112 (24.1%)	7/108 (6.5%)	17.6% (8.4%, 26.8%)
	Day 15	51/112 (45.5%)	14/108 (13.0%)	32.5% (21.4%, 43.8%)
Study 2	Day 8	33/110 (30.0%)	14/110 (12.7%)	17.3% (6.7%, 27.9%)
	Day 15	50/ 110 (45.4%)	30/ 110 (27.3%)	18.2% (5.7%, 30.7%)
			Pain Free	
Study 1	Day 1	91/112 (81.3%)	47/108 (43.5%)	37.7 %(25.9%, 49.6%)
Study 2	Day 1	84/110 (76.4%)	61/110 (55.5%)	20.9% (8.7%, 33.1%)

6 Appendix

Table 55: SOIS Score at Different Days

Study	Subject ID	SOIS Score at Different Days				ARM
		Day 1	Day 3	Day 8	Day 15	
S00124-ER	6107	0	1.5	1.5	0.5	Bromfenac
	6801	4	0	0.5	0.5	Bromfenac
	7501	2	2	0	0.5	Bromfenac
	5001	1.75	1.5	0	1.5	Placebo
	5015	1.5	0	1.5	0.5	Placebo
	6106	1.5	1.5	0	1.5	Placebo
	7305	3	1.5	0	1.5	Placebo
S00124-WR	0709	0.5	0.5	0	0.5	Bromfenac
	1308	2	0	1.5	1.25	Bromfenac
	2302	2	0.5	0	0.5	Bromfenac
	2317	2	0.5	0	0.25	Bromfenac
	0401	2	0.5	0	0.5	Placebo
	0413	1.75	0.5	0	1.5	Placebo
	1005	3	3	0	1	Placebo
	1709	0.25	0.5	0	0.5	Placebo

Table 56: Average Anterior Chamber Cell Grades at Different Days

Study	Subject ID	Average Cells Grade at Different Days				ARM
		Day 1	Day 3	Day 8	Day 15	
S00124-ER	6107	0	0.5	0.5	0.5	Bromfenac
	6801	2	0	0.5	0.5	Bromfenac
	7501	2	2	0	0.5	Bromfenac
	5001	0.75	0.5	0	0.5	Placebo
	5015	0.5	0	0.5	0.5	Placebo
	6106	0.5	0.5	0	0.5	Placebo
	7305	1	0.5	0	0.5	Placebo
S00124-WR	0709	0.5	0.5	0	0.5	Bromfenac
	1308	1	0	0.5	0.25	Bromfenac
	2302	1	0.5	0	0.5	Bromfenac
	2317	1	0.5	0	0.25	Bromfenac
	0401	1	0.5	0	0.5	Placebo
	0413	0.75	0.5	0	0.5	Placebo
	1005	2	2	0	1	Placebo
	1709	0.25	0.5	0	0.5	Placebo

Source: Reviewer's analysis. These subjects were treated as success in the applicant's analysis. The reviewer's analysis treats these subjects as failures.

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

/s/

ABEL T ESHETE
03/04/2013

YAN WANG
03/04/2013
I concur. See my review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203168	**Applicant:** ISTA Pharmaceuticals, Inc.	**Stamp Date:** June 7, 2012
Drug Name: (b) (4) (bromfenac ophthalmic solution) 0.07%	**NDA Type:** Standard Review	**Indication:** Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery

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

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

The NDA is fileable from the statistical perspective. However, the following issues were noted during the preliminary review.

1. During our preliminary review, we were able to replicate the majority of efficacy analyses results reported by the applicant. We however were not able to replicate the results of the sensitivity analyses using multiple imputations to handle missing data conducted by the applicant. For the safety analysis, we have noticed slight discrepancies between our analysis and that of the applicant. The applicant did not conduct safety and efficacy analysis for gender, racial, and geriatric subgroups. We were not also able to locate the program codes used to generate the table and listings. They applicant has some programs included in the submission but we were not able to run and generate their results.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	✓			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	✓			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			✓	
Appropriate references for novel statistical methodology (if present) are included.			✓	
Safety data organized to permit analyses across clinical trials in the NDA.	✓			#1
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	✓			#1

We have the following information request for the applicant:

1. We were not able to locate the program codes you used to generate the tables and listings for study S00124-ER and study S00124-WR and for the ISE and ISS reports. Please submit these program codes with a detailed documentation. These program codes will help us to reproduce and evaluate your results, and expedite our review of your NDA. For example, without access to your SAS program "t1402010504.sas", which was indicated in the footnote for Table 14.2.1.5.4 on page 299 of your study report for study S00124-ER, we cannot evaluate your analysis results based on the multiple imputation approach.
2. Please conduct safety and efficacy analysis for gender, racial, and geriatric subgroups for study S00124-ER and study S00124-WR in the same manner as you did for ISE and ISS reports.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials

This application provides data from two phase 3 studies (CL-S&E-0415081-P-ER and CL-S&E-0415081-P-WR) to support the safety and efficacy of Bromfenac 0.07% Ophthalmic Solution in the treatment of Ocular Inflammation and Pain Associated with Cataract Surgery. The following tables contain information on the relevant trials contained in the submission.

Study number	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
CL-S&E-0415081-P-ER	A multi-center, randomized, double-masked, parallel group and placebo (vehicle) controlled study. to evaluate the efficacy and safety of Bromfenac 0.07% Ophthalmic Solution for Treatment of Ocular Inflammation and Pain Associated with Cataract Surgery	– Bromfenac 0.07% Ophthalmic Solution; N=112 – Placebo; N=108 Note: Bromfenac group will instill one drop of investigational product into the study (operative) eye once daily for a maximum of 16 days. Dosing with investigational product will begin one day prior to surgery (Day -1); continue on the day of surgery and for 14 days after surgery. Placebo group will instill one drop of placebo into the study (operative) eye once daily for a maximum of 16 days. Dosing with investigational product will begin one day prior to surgery (Day -1), continue on the day of surgery and for 14 days after surgery.	Primary: The proportion of subjects with cleared ocular inflammation by Day 15, which is defined as a summed ocular inflammation score (SOIS) of grade 0 (0 cells and absence of flare) at any post-surgery visit prior to and including Day 15. Key secondary: The proportion of subjects that are pain free (i.e., pain grading of 'None' on the Ocular Comfort Grading Assessment) at Day 1. The primary analysis was a statistical evaluation of superiority of Bromfenac 0.07% Ophthalmic Solution to placebo with respect to the primary efficacy variable. A 2-sided Fisher's Exact test at alpha level of 5% was performed.	The proportion of subjects who had cleared ocular inflammation by Day 15 was 48.2% in the Bromfenac 0.07% group versus 16.7% in the placebo group ($p<0.001$), demonstrating superiority of Bromfenac 0.07% to the placebo group. The proportion of subjects that are pain free (i.e., pain grading of 'None' on the Ocular Comfort Grading Assessment) at Day 1 was 81.3% in the Bromfenac 0.07% group versus 43.5% in the placebo group ($p<0.001$).
CL-S&E-0415081-P-WR	– A multi-center, randomized, double-masked, parallel group and placebo (vehicle)	– Bromfenac 0.07% Ophthalmic Solution; N=110 Placebo; N=110 Note: Bromfenac group will instill one drop of investigational product into the study (operative) eye once daily for a	Primary: The proportion of subjects with cleared ocular inflammation by Day 15, which is defined as a summed ocular inflammation score (SOIS) of grade 0 (0 cells and absence of flare) at any post-surgery visit prior to and including Day 15.	The proportion of subjects who had cleared ocular inflammation by Day 15 was 49.1% in the Bromfenac 0.07% group versus 31.8% in the placebo group ($p=0.0132$), demonstrating superiority of

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Study number	Design	Treatment/Sample size	Endpoint/Analysis	Applicant's findings
	controlled study. to evaluate the efficacy and safety of Bromfenac 0.07% Ophthalmic Solution for Treatment of Ocular Inflammation and – Pain Associated with Cataract Surgery	maximum of 16 days. Dosing with investigational product will begin one day prior to surgery (Day -1); continue on the day of surgery and for 14 days after surgery. – Placebo group will instill one drop of placebo into the study (operative) eye once daily for a maximum of 16 days. Dosing with investigational product will begin one day prior to surgery (Day -1), continue on the day of surgery and for 14 days after surgery.	Key secondary: The proportion of subjects that are pain free (i.e., pain grading of 'None' on the Ocular Comfort Grading Assessment) at Day 1. The primary analysis was a statistical evaluation of superiority of Bromfenac 0.07% Ophthalmic Solution to placebo with respect to the primary efficacy variable. A 2-sided Fisher's Exact test at alpha level of 5% was performed.	Bromfenac 0.07% to the placebo group. The proportion of subjects that are pain free (i.e., pain grading of 'None' on the Ocular Comfort Grading Assessment) at Day 1 was 76.4% in the Bromfenac 0.07% group versus 55.5% in the placebo group (p=0.0017).

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Table 1. Patient Disposition

	STUDIES			
	CL-S&E-0415081-P-ER		CL-S&E-0415081-P-WR	
	Bromfenac 0.07% n (%)	Placebo n (%)	Bromfenac 0.07% n (%)	Placebo n (%)
Number of Subjects Randomized	112(100%)	108(100%)	110(100%)	110(100%)
Subjects who completed the study [1]	109(97.3%)	102(94.4%)	104(94.5%)	100(90.9%)
Primary Reason for Early Termination				
Withdrawal of Consent/Non-Compliance	2(1.8%)	3(2.8%)	4(3.6%)	3(2.7%)
Lost to Follow-UP	0	0	0	0
Death	0	0	0	0
Other [2]	1(0.9%)	3(2.8%)	2(1.8%)	7(6.4%)
Subjects Who Discontinue IP Early	11(9.8%)	47(53.5%)	23(20.9%)	49(44.5%)
Reason for Early IP Discontinuation:				
Adverse Event	4(3.6%)	3(2.8%)	7(6.4%)	26(23.6%)
Disallowed Concurrent Medication	0	0	2(1.8%)	2(1.8%0
Lack of Efficacy	2(1.8%)	37(34.3%)	5(4.5%)	15(13.6%0
Other [3]	5(4.5%)	7(6.5%)	9(8.2%)	6(5.5%)
Visit Completed (ITT population)				
Day1	108(96%)	102(94.4%)	102(92.7%)	99(90.0%)
Day3	105(93.8%)	101(93.5%)	00(90.0%)	96(87.3%)
Day8	100 (89.3%)	72(66.7%)	93 (84.5%)	83(75.5%)
Day 15	100 (89.3%)	59(54.6%)	87 (79.1%)	60(54.5%)
Day 22	109 (97.3%)	102(94.4%)	104(94.5%)	100(90.9%)

Source: Tables 4-6 of Applicant's submitted Study Reports

[1] : A visit was considered complete if at least 1 procedure was performed

[2] **:** Other reasons for early discontinuation of the study include : For Study S00124ER :Inappropriate Randomization (1 subject), surgery cancelled(1 subjects), did not meet exclusion criteria (1 subjects); For Study S00124WR: cancelled surgery(4 subjects), disallowed medication at enrollment(2 subjects), experience of SAE (subjects), inappropriate randomization (1 subject)

[3] **:** Other reasons for early discontinuation of the study include : For Study S00124ER : Withdrawal of consent/non-compliance (6 subjects), never used IP(2 subjects), cancelled surgery(2 subjects), Incorrect screening period/visit outside of Windows(2 subjects) : For Study S00124WR: cancelled surgery(5 subjects), Withdrawal of consent (5 subjects), ran out of IP (1 subject), discontinued IP (1 subject), lost of IP (1 subject), randomization error(1 subject)

Table 2. Baseline Demographics (ITT population)

	STUDIES					
	CL-S&E-0415081-P-ER			CL-S&E-0415081-P-WR		
	Bromfenac 0.07% N=112	Placebo N=108	Total N=220	Bromfenac 0.07% N=110	Placebo N=110	Total N=220
Age(years)						
Mean (SD)	67.2(10.52)	67.6(10.07)	67.4(10.28)	69.6(10.79)	69.4 (9.24%)	69.5(10.02%)
Range	39-87	40-85	39-87	18-93	46-90	18-93
Gender (n, %)						
Male	41(36.6%)	40(37.0%)	81 (36.8%)	40(36.4%)	32(29.1%)	72(32.7%)
Female	71(63.4%)	68(63.0%)	139 (63.2%)	70(63.6%0	78(70.9%)	148(67.3%)
Race (n, %)						
American Indian or Alaskan Native	0	0	0	1(0.9%)	0	1(0.5%)
Asian	0	1(0.9%)	1 (0.5%)	4 (3.6%)	7(6.4%)	11(5.0%)
Black or African American	13(11.6%)	8(7.4%)	21 (9.5%)	9(8.2%)	9(8.2%)	18(8.2%)
Native Hawaiian or Other Pacific highlander	0	0	0	0	0	0
White	88(78.6%)	91 (84.3%)	179(81.4%)	79(71.8%)	71(64.5%)	150(68.2%)
Other	11(9.8%)	8(7.4%)	19(8.6%)	17(15.5%)	23(20.9%)	40(18.2%)
Iris Color (Study eye) (n, %)						
Black	0	0	0	0	0	0
Blue	28(25.0%)	36(33.3%)	64 (29.1%)	29(26.4%)	29(26.4%)	58(26.4%)
Brown	57 (50.9%)	39(36.1%0	96(43.6%)	52 (47.3%)	54(49.1%)	106(48.2%0
Gray	0	4(3.7%0	4(1.8%0	1(0.9%)	1(0.9%)	2(0.9%)
Green	8(7.1%)	12(11.1%)	20(9.1%)	16(14.5%)	9(8.2%)	25(11.4%)
Hazel	19(17.0%)	17(15.7%)	36(16.4%)	12 (10.9%)	16(14.5%)	28(12.7%)
Other	0	0	0	0	1(0.9%)	1(0.5%)
Iris Color (Study eye) (n, %)						
Light Irides	47(42.0%)	57(52.8%)	104(47.3%)	42(38.2%)	47(42.7%)	89(40.5%)
Dark Irides	65(58.0%)	51(47.2%)	116(52.7%)	68(61.8%)	63(57.3%)	131(59.5%)

Source: Tables 7 of Applicant's submitted Study Reports

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Table 3: SOIS Grade 0 *by* each Visit (LOCF Analysis: ITT population)

Cleared Ocular Inflammation[1]	STUDIES					
	CL-S&E-0415081-P-ER			CL-S&E-0415081-P-WR		
	Bromfenac 0.07% N=112	Placebo N=108	P-value	Bromfenac 0.07% N=110	Placebo N=110	P-value
Day 1	2(1.8%)	0 (0.0%)	0.4979[2]	3(2.7%0	4(3.6%)	>0.9999[2]
Day 3	7(6.3%)	1(0.9%)	0.1314[2]	8(7.3%)	7(6.4%)	>0.9999[2]
Day 8	30(26.8%)	8(7.4%)	0.0006[2]	36(32.7%)	18(16.4%)	0.0370[2]
Day 15	54(48.2%)	18(16.7%)	<0.0001[3]	54(49.1%)	35(31.8%)	0.0132[3]
Day 22	74(66.1%)	57(52.8%)	0.1314[2]	81(73.6%)	63(57.3%)	0.0470[2]

Source: Tables 8 of Applicant's submitted Study Reports

[1] : Cleared ocular inflammation by each visit is defined as a SOIS of Grade 0 at or prior to each visit.

[2] : P-value is for Bromfenac 0.07% versus placebo and was from Fisher's exact test adjusted for multiple comparisons using Hocheberg's method.

[3] : Primary Efficacy endpoint, P-value is for Bromfenac 0.07% versus placebo and was from Fisher's exact test (Note: Not adjusted).

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewing Statistician	Date
Supervisor/Team Leader	Date

Page 8 of 8

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

/s/

ABEL T ESHETE
07/18/2012

YAN WANG
07/18/2012