

**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 Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22-427 (original)

**Drug Name:** ACUVAIL (ketorolac tromethamine ophthalmic solution) 0.45%

**Indication(s):** Treatment of post-operative pain and inflammation in patients who have undergone cataract extraction

**Applicant:** Allergan, Inc.

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## **1. EXECUTIVE SUMMARY**

In this submission, the sponsor is seeking approval for Ketorolac Tromethamine 0.45% ophthalmic solution for the treatment of inflammation and pain associated with cataract surgery. The sponsor has submitted two phase 3 studies (Study 191578-005 and Study 191578-006) which compared the efficacy and safety of Ketorolac Tromethamine 0.45% Ophthalmic solution with vehicle administered preoperatively and twice daily. In both studies, the primary efficacy endpoint was based on the proportion of patients with clearing of anterior chamber inflammation on day 14 in the operative eye. Note that clearing of anterior chamber inflammation is indicated by the summed ocular inflammation scores (SOIS) equal to zero.

### **1.1 Conclusions and Recommendations**

In both studies, the efficacy data demonstrated that the new formulation of Ketorolac 0.45% was statistically significantly superior to vehicle in clearing of anterior chamber inflammation. In study 191578-005, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population was 69/149(46.3%) in the ketorolac 0.45% arm versus 20/78(25.6%) in the vehicle arm (p-value=0.0025). In study 191578-006, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population was 98/169(58.0%) in the ketorolac 0.45% arm versus 21/77(27.3%) in the vehicle arm (p-value<0.0001).

In addition, Ketorolac 0.45% demonstrated statistical significance to vehicle in one of the secondary endpoint of the resolution of ocular pain in both studies. The other secondary endpoint of mean pupil area measured post- irrigation and aspiration (I&A) failed to demonstrate statistical significance in both studies.

According to sponsor's reporting of safety issues, patients receiving ketorolac 0.45% had a lower incidence of ocular adverse events than patients receiving vehicle in both studies,. More details on safety can be obtained from the clinical review.

### **1.2 Brief Overview of Clinical Studies**

Study 191578-005 and Study 191578 006 were conducted to evaluate the safety and efficacy of ketorolac eye drops for the treatment of inflammation and pain associated with cataract surgery. Both studies were multicenter, randomized, double masked and parallel group comparison studies. Each study assessed the safety and efficacy of ketorolac 0.45% compared with vehicle administered preoperatively and postoperatively in the treatment of anterior segment inflammation, pain, and inhibition of surgically induced miosis following cataract extraction with posterior chamber intraocular lens (IOL) implantation. Patients underwent 7 scheduled visits which include a screening visit (week -4 to day -2), randomization (day -3 to day -1), cataract surgery day, day 1, day 3, day 7, and day 14 or study exit visit.

In both studies, the primary efficacy variable was the proportion of patients with the clearing of anterior chamber inflammation; i.e., SOIS (summed ocular inflammation scores) equal to 0, in the operative eye. The primary efficacy analysis was the comparison between ketorolac 0.45% and vehicle on the primary efficacy variable on day 14 using the mITT population.

Approximately 225 patients were planned (for each study) to be randomized with a 2:1 ratio of treatment allocation in order to study approximately 201 evaluable patients with inflammation in the operative eye after surgery. Informed consent was obtained and screening procedures were performed at the screening visit.

### 1.3 Statistical Issues and Findings

Last observation carried forward (LOCF) was used for imputing missing values. There are concerns in using LOCF which can potentially bias the results. Furthermore, the sponsor did not include all the mITT patients in the mITT-LOCF analysis. According to sponsor, no imputation could be done for missing data on day 1 (refer to methods of analysis and multiplicity assessment under subsection 3.1.3) and hence this reviewer performed sensitivity analysis by classifying the missing values as failures for those patients who were not included in the sponsor's mITT-LOCF analysis.

In study 191578-005, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population, was 69/149(46.3%) in the ketorolac 0.45% arm versus 20/78(25.6%) in the vehicle arm (p-value=0.0025). The MITT population as reported in Table 2, there were 155 patients in the Ketorolac arm versus 79 patients in the vehicle arm. This reviewer has conducted a sensitivity analysis by classifying unreported patients' outcomes as failures (i.e. SOIS>0) in both groups. The efficacy conclusions did not change based on the sensitivity analysis 69/155(44.52%) for Ketorolac 0.45% vs. 20/79(25.32%) for the vehicle; p-value is 0.0042(chi-square test).

In study 191578-006, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population, was 98/169(58.0%) in the ketorolac 0.45% arm versus 21/77(27.3%) in the vehicle arm (p-value<0.0001). The MITT population as reported in Table 3, there were 173 patients in the Ketorolac arm versus 82 in the vehicle arm. Based on the sensitivity analysis by classifying unreported outcomes as failures (i.e. SOIS>0) in both groups, the efficacy conclusions did not change. The rates for Ketorolac and vehicle arms were 98/173(56.65%) and 21/82(25.61%) respectively; p-value:<0.0001 (chi-square test).

The interaction effect was also evaluated between treatment by subgroups such as gender, race and age. The Breslow and Day test has not detected any significant interaction effect between treatment by subgroups for study 191578-005. However, in study 191578-006, the Breslow and Day test has detected interaction effect (p-value=0.0097) between treatment by race subgroup (Caucasian vs. non-Caucasian). Note that the presence of interaction indicates that the treatment benefit is different in the two subgroups. Although there is differential effect for the treatment

due to race, it is going in the same direction demonstrating statistical significance of superiority for ketorolac 0.45% over vehicle for the primary endpoint. However, because of small sample size in non-Caucasian patient group, the interpretation of interaction effect is limited.

## **2. INTRODUCTION**

In this submission, the sponsor is seeking approval for Ketorolac Tromethamine 0.45% ophthalmic solution for the treatment of inflammation and pain associated with cataract surgery. The sponsor has submitted two phase 3 studies (Study 191578-005 and Study 191578-006) which compared the efficacy and safety of Ketorolac Tromethamine 0.45% Ophthalmic solution with vehicle administered preoperatively and twice- daily. In both studies, the primary efficacy endpoint was based on the proportion of patients with clearing of anterior chamber inflammation on day 14 in the operative eye. Note that clearing of anterior chamber inflammation is indicated by the summed ocular inflammation scores (SOIS) equal to 0.

### **2.1 Specific Studies Reviewed**

This reviewer focused on the review of two phase 3 studies (Study 191578-005 and Study 191578-006). The primary objective of this study was to evaluate the efficacy of ketorolac 0.45% compared with vehicle for clearing anterior segment inflammation following cataract extraction with posterior chamber intraocular lens implantation.

The secondary objectives are to evaluate the efficacy of ketorolac 0.45% compared with vehicle in the resolution of postoperative pain and to inhibit miosis during cataract surgery. In addition the safety of ketorolac 0.45% compared with vehicle was also evaluated.

### **2.2 Data Sources**

The data sets were adequately documented and generally represented the data described in the study reports. Data sets and all modules containing clinical study reports were submitted electronically. The full electronic path for the submission is \\CDSESUB1\EVSPROD\NDA022427\

## **3. STATISTICAL EVALUATION**

### **3.1 Evaluation of Efficacy**

In this subsection, we evaluated the efficacy of ketorolac 0.45% compared with vehicle administered preoperatively and postoperatively in the treatment of ocular inflammation and pain following cataract surgery.

#### **3.1.1 Study Design and Endpoints**

Studies 191578-005 and 191578-006 were multicenter (22 centers in study 191578-005 and 26 centers in study 191578-006), randomized, double-masked and parallel group comparison study.

Both studies assessed the safety and efficacy of ketorolac 0.45% compared with vehicle administered preoperatively and postoperatively in the treatment of anterior segment inflammation, pain, and inhibition of surgically induced miosis following cataract extraction with posterior chamber intraocular lens (IOL) implantation. Each study consisted of 7 scheduled visits: screening (week -4 to day -2), randomization (day -3 to day -1), cataract surgery day, day 1, day 3, day 7, and day 14 or study exit.

Qualified patients were randomized to either ketorolac 0.45% or vehicle at the randomization visit (day -3 to day -1). Since ketorolac 0.45% is a non-preserved, unit dose ophthalmic solution, to ensure masking, all study medication was labeled for single use and packaged in sterile single-use containers. Patients were instructed to begin twice daily (BID) dosing of study medication in the operative eye the day before surgery (day -1) and to continue dosing on the day of surgery and day 1 through day 14 as per the protocol.

Approximately 225 patients were planned (for each study) to be randomized with a 2:1 ratio (ketorolac : vehicle) of treatment allocation in order to study approximately 201 patients with an evaluation of Inflammation in the operative eye after surgery. According to the sponsor, informed consent was obtained and screening procedures were performed at the screening visit.

### ***Randomization***

Prior to initiation of study treatment, each patient who qualified for study entry was assigned a patient number that was recorded in the source documents, then on the appropriate electronic case report form (eCRF). At the time of randomization (day -3 to day -1), a randomization number was assigned to patients sequentially according to the order of enrollment within each site. An automated IVRS/Interactive Web Response System (IWRS) was used to manage the randomization and the treatment assignment based on the randomization scheme prepared by Allergan Biostatistics team.

***Primary Efficacy Measurement:***

In both studies, anterior chamber inflammation assessment in the operative eye was performed on day 14. The SOIS (summed ocular inflammation scores) for a patient was calculated as the sum of the score for anterior chamber cells and the score for anterior chamber flare in the operative eye of the patient (see grade scale table below).

**Table 1: Ocular Inflammation Grade Scale**

Anterior Chamber Cells		Anterior Chamber Flare	
Grade Score	Cell Count	Grade Score	Flare
0	0 cells	0	None: No flare seen
+0.5	1–5 cells (trace)	+1	Faint: Faint flare seen
+1	6–15 cells	+2	Moderate: Iris and lens details clear
+2	16–25 cells	+3	Marked: Iris and lens details hazy
+3	26–50 cells	+4	Intense: Fibrin or plastic aqueous
+4	>50 cells		

Sponsor's table

***Secondary Efficacy Measurements:***

In both studies, the following secondary efficacy measures were evaluated:

- Ocular pain as measured by a twice daily self-assessment by the patient within approximately 1 hr after dosing using a 5-point grade scale (0 = none, +1 = mild, +2 = moderate, +3 = severe, +4 = intolerable) was assessed. The percentage of patients with no pain (grade = 0) on day 1 was evaluated as a secondary efficacy analysis.
- Horizontal and vertical pupil diameters were measured immediately pre-incision, post-I&A of the lens, and after IOL placement. The mean pupil area post-I&A of the lens was evaluated as a secondary efficacy analysis.

***Determination of Sample Size:***

In both studies, sample size and power calculations were based on the comparison on day 14 of the primary efficacy variable of clearing anterior chamber inflammation and of the secondary variables of freedom from ocular pain on day 1 and pupil area post-I&A of the lens.

According to the sponsor, in the original study protocol, 200 patients were planned to be randomized. The planned sample size was increased to 225 randomized patients in Amendment 2.0 to the study protocol, to ensure adequate power (i.e., at least 80%) to demonstrate efficacy



for the two phase 3 studies (191578-005 and 191578-006) and to minimize the risk of a Type II error.

The power calculation for clearing of anterior chamber inflammation and freedom from pain used procedure was based on a 2-sided Pearson's chi-square test with a continuity correction and for unequal sample sizes. A 2-group t-test for the equality of means was used for the pupil area power calculation with unequal sample sizes.

***Analysis Populations:***

Four analysis populations were used this study: the intent-to treat (ITT), modified intent-to-treat (mITT), per protocol (PP), and safety populations. All exit status and demographic data and some efficacy data were analyzed using the ITT population, which includes all randomized patients. Analyses using this population were based on the treatment to which the patient was randomized. The efficacy data were analyzed using the mITT and PP populations. The mITT population included all randomized patients who underwent cataract extraction surgery with posterior chamber IOL implantation in the operative eye. The PP population included all mITT patients with no major protocol deviations. PP exclusions were determined prior to the database lock. The safety population, which included all randomized patients who received at least 1 dose of study medication, was used to analyze all safety data. Safety analyses were based on the actual treatment that the patients received.

***Protocol Amendments: Changes in the Conduct of the Study:***

Two amendments were made to the study protocol after the beginning of patient enrollment, Amendment 1.0 (October 2007) and Amendment 2.0 (December 2007). Amendment 1.0 contained some clarifications and corrections to the original study protocol. Most importantly, the handling of patients with rescheduled cataract surgery was specified. Amendment 2.0 included an increase in sample size and some changes to the planned analyses.

### 3.1.2 Subject Disposition, Demographic and Baseline Characteristics

#### 3.1.2.1 Subject Disposition

##### *Study 191578-005:*

The following table summarizes disposition of patients in Study 191578-005:

**Table 2: Patient Disposition**

<b>Patient Population</b>	<b>Ketorolac 0.45% (# of patients)</b>	<b>Vehicle (# of patients)</b>	<b>Total (# of patients)</b>
ITT	164	84	248
Completed	144 (87.8%)	57 (67.9%)	201 (81.0%)
Modified ITT	155	79	234
Per-Protocol	125	59	184
Safety	157	81	238

It can be seen from the above table that a total of 248 patients were randomly assigned to two treatment groups (164 assigned to ketorolac 0.45% and 84 assigned to vehicle) in this study. A higher percentage of patients 87.8% (144/164) in the ketorolac 0.45% group than 67.9% (57/84) in the vehicle group completed the study.

##### *Study 191578-006*

The following table summarizes disposition of patients in Study 191578-006:

**Table 3: Patient Disposition**

<b>Patient Population</b>	<b>Ketorolac 0.45% (# of patients)</b>	<b>Vehicle (# of patients)</b>	<b>Total (# of patients)</b>
ITT	176	87	263
Completed	163 (92.65)	59 (67.8%)	222 (84.4%)
Modified ITT	173	82	255
Per-Protocol	161	75	236
Safety	173	82	255

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It can be seen that a total of 263 patients were randomly assigned to treatment in this study, including 176 assigned to ketorolac 0.45% and 87 assigned to vehicle. A higher percentage of patients 92.6% (163/176) in the ketorolac 0.45% group than 67.8% (59/87) in the vehicle group, completed the study.

### 3.1.2.2 Baseline Characteristics

#### *Study 191578-005:*

The following table summarizes the patients' demographics and baseline characteristics for the intent-to-treat population

**Table 4: Demographics and Baseline Characteristics (Intent-to-Treat Population)**

<b>Characteristics</b>	<b>Ketorolac 0.45% (# of patients: 164)</b>	<b>Vehicle (# of patients: 84)</b>	<b>Total (# of patients: 248)</b>
<b>Age in years:</b>			
Mean	68.9	67.6	68.4
Median	70.0	68.5	70.0
<b>Gender:</b>			
Male	72 (43.9%)	35 (41.7%)	107 (43.1%)
Female	92 (56.1%)	49 (58.3%)	141 (56.9%)
<b>Race</b>			
Caucasian	149 (90.8%)	71(84.5%)	220(88.7%)
Black	2 (1.2%)	2(4.8%)	6(2.4%)
Asian	1(0.6%)	2(2.4%)	3(1.2%)
Hispanic	11(6.7%)	7(8.3%)	18(7.3%)
Other	1(0.6%)	0(0.0%)	1(0.4%)
<b>Iris Color:</b>			
Blue	56 (34.1%)	30(35.7%)	86 (34.7%)
Green	5(3.0%)	2(2.4%)	7(2.8%)
Hazel	40(24.4%)	18(21.4%)	58(23.4%)
Brown	59(36.0%)	34(40.5%)	93(37.5%)
Other	4 (2.4%)	0(0.0%)	4(1.6%)

It can be seen from the above table that demographic and other baseline characteristics were similar across the 2 treatment groups. Majority of patients were being >65 years of age (65.9% [108/164] of the ketorolac 0.45% group and 58.3% [49/84] of the vehicle group). More than half

of the patients in the study were women (56.9% [141/248]) and most of the patients were Caucasian (88.7% [220/248]). Most of the patients had brown (37.5% [93/248]) or blue (34.7% [86/248]) eyes.

**Study 191578-006:**

The following table summarizes the patients' demographics and baseline characteristics for the intent-to-treat population:

**Table 5: Demographics and Baseline Characteristics (Intent-to-Treat Population)**

Characteristics	Ketorolac 0.45% (# of patients: 176 )	Vehicle (# of patients: 87)	Total (# of patients: 263)
Age in years:			
Mean	68.5	66.7	67.9
Median	70.0	68.0	69.0
Gender:			
Male	75(42.6%)	36(41.4%)	111(42.2%)
Female	101(57.4%)	51(58.6%)	152(57.8%)
Race:			
Caucasian	146 (83.0%)	70(80.5%)	216(82.1%)
Black	2 (1.1%)	5(5.7%)	7(2.7%)
Asian	1(0.6%)	0(0.0%)	1(0.4%)
Hispanic	23 (13.1%)	12(13.8%)	35(13.3%)
Other	4(2.3%)	0(0.0%)	4(1.5%)
Iris Color:			
Blue	57 (32.4%)	31(35.6%)	88(33.5%)
Green	4(2.3%)	10(11.5%)	14(5.3%)
Hazel	30(17.0%)	17(19.5%)	47(17.9%)
Brown	83(47.2%)	29(33.3%)	119(42.6%)
Other	2(1.1%)	0(0.0%)	2(0.8%)

It can be seen from the above table, other than iris color, demographic and other baseline characteristics were similar across the 2 treatment groups. A little more than half of the patients in the study were women (57.8% [152/263]) and most of the patients were Caucasian (82.1% [216/263]). Majority of patients were being > 65 years of age (65.9% [116/176] of the ketorolac 0.45% group and 59.8% [52/87] of the vehicle group). Most of the patients had brown (42.6% [112/263]) or blue (33.5% [88/263]) eyes. Distribution of iris color in the ketorolac 0.45% group was nearly equal between dark and light (47.2% [83/176] dark and 52.8% [93/176] light) whereas distribution in the vehicle group was in the ratio of 1:2 dark: light (33.3% [29/87] dark and 66.7% [58/87] light). The sponsor reported that the distribution of dark and light iris color was significantly different between the 2 groups (p-value = 0.033).

### 3.1.3 Statistical Methodology

#### Primary Efficacy Endpoints:

##### *Primary Efficacy Analysis*

In both studies, the primary efficacy variable was the proportion of patients with the clearing of anterior chamber inflammation; i.e., SOIS score equal to 0 in the operative eye. The primary efficacy analysis was the comparison between ketorolac 0.45% and vehicle on the primary efficacy variable on day 14 for the mITT population.

##### *Secondary Efficacy Analyses*

In both studies, secondary efficacy variables included the proportion of patients with no postoperative ocular pain (i.e., grade of pain = 0) at both the morning and evening evaluation on day 1. Inhibition of Ketorolac tromethamine ophthalmic solution 0.45% surgically induced miosis was also measured by the pupil area after I&A of the lens. Both secondary efficacy analyses were performed using the mITT population.

#### Methods of Analysis and Multiplicity Assessment:

For the primary efficacy analyses, the null hypothesis was that there was no between-group difference in the proportion of patients with an SOIS of 0. The alternative hypothesis was that there was a between-group difference in the proportion of patients with an SOIS of 0. The analysis was performed using a 2-sided Pearson's chi-square test. A p-value of  $\leq 0.05$  was considered statistically significant.

To control the overall type I error at 0.05 in the analyses of the 2 secondary variables, a gate keeping approach was used. The significance level for each analysis was 0.05 and the method described below was followed:

Step 1: A between-group comparison was performed on the proportion of patients who had freedom from ocular pain on day 1 (morning and evening) using a 2-sided Pearson's chi-square test. If the treatment effect was statistically significant ( $p \leq 0.05$ ), analysis for pupil size post-irrigation and aspiration (I&A) of lens was performed as outlined in Step 2; otherwise no further testing for pupil area was performed.

Step 2: A between-group comparison was performed of the pupil area (post-I&A of lens) using a 1-way analysis of variance (ANOVA) test.

The last observation carried forward (LOCF) method was used to impute missing data; however, no imputation could be done for missing data on day 1. In the event that a patient used any supplemental medication to control inflammation after surgery (prohibited medication), the SOIS observed after taking such medications was considered missing, and the LOCF method was used to impute the data. In addition, if a topical or oral steroid, or a topical or oral non-study NSAID was taken before the cataract surgery day, the patient was to be withdrawn from the study and the scores collected on day 1 were considered missing. Supplemental medications fitting into this category were determined prior to the database lock.

### 3.1.4 Results and Conclusions

#### *Primary Efficacy Analysis*

#### *Study 191578 -005:*

The following table summarizes the efficacy results for Ketorolac 0.45% versus vehicle.

**Table 6: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14**

Day 14	Ketorolac 0.45% (N=149)	Vehicle (N=78)	P-value (Chi-square)
Yes	69/149(46.3%)	20/78 (25.6%)	0.0025
No	80 /149(53.7%)	58/78(74.4%)	

It can be seen from the above table that for the primary efficacy endpoint, 46.3% (69/149) of patients receiving ketorolac 0.45% had clearing of anterior chamber inflammation (SOIS = 0) at day 14 compared to 25.6% of patients receiving vehicle (20/79) in the MITT population. It can be concluded that ketorolac 0.45% is significantly more effective in clearing of anterior chamber inflammation (p-value = 0.0025).

#### *Statistical Reviewer's Comments:*

1. To see the robustness of the efficacy results, this reviewer conducted Fisher's exact test. The Fisher's exact test showed that Ketorolac 45% had significantly (p-value 0.0027) higher rate of clearing of interior chamber inflammation than vehicle. The efficacy conclusions remain the same in comparison to the chi-square test.

2. The MITT population as reported in Table 2, there were 155 patients in the Ketorolac arm versus 79 patients in the vehicle arm. This reviewer has conducted a sensitivity analysis by classifying unreported patients' outcomes as failures (i.e. SOIS > 0) in both groups. The efficacy conclusions did not change based on the sensitivity analysis (69/155(44.52%) for Ketorolac 0.45% vs. 20/79(25.32%) for the vehicle; chi-square test's p-value: 0.0042.

#### *Sensitivity Analyses:*

For the ITT population, when missing SOIS were classified as failures (i.e., SOIS not equal to 0), patients receiving ketorolac 0.45% had a statistically significantly higher incidence of clearing of anterior chamber inflammation (SOIS = 0) compared to patients receiving vehicle at day 14 (69/164(42.1% vs. 20/84(23.81%); p-value = 0.005).

## Secondary Efficacy Analyses

### *Ocular Pain Resolution:*

There was a statistically significantly greater proportion of patients who were ocular pain-free at day 1 in the ketorolac 0.45% group, 75.0% (114/152 patients), compared to the vehicle group, 41.0% (32/78 patients) (p-value < 0.001)

### *Inhibition of Surgically Induced Miosis:*

The mean pupil area measured post-I&A was not statistically significantly different between the two treatment groups (p-value= 0.706). Mean pupil area post-I&A was 41.8 mm<sup>2</sup> in the ketorolac 0.45% group and 41.1 mm<sup>2</sup> in the vehicle group.

### **Study 191578 -006:**

The following table summarizes the efficacy results for Ketorolac 0.45% versus vehicle.

**Table 7: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Yes	98/169(58.0%)	21/77(27.3%)	<0.0001
No	71/169 (42.0%)	56/77(72.7%)	

It can be seen from the above table that for the primary efficacy endpoint, 58.0% (98/169) of patients receiving ketorolac 0.45% had clearing of anterior chamber inflammation (SOIS = 0) at day 14 compared to 27.3 of patients receiving vehicle (21/77) in the mITT population. It can be concluded that ketorolac 0.45% is significantly more effective in clearing of anterior chamber inflammation (p-value < 0.0001).

### **Statistical Reviewer's Comments:**

1. To see the robustness of the efficacy results, this reviewer conducted Fisher's exact test. The Fisher's exact test showed that Ketorolac 45% had significantly (p-value < 0.0001) higher rate of clearing of interior chamber inflammation than vehicle. The efficacy conclusions remain the same in comparison to the chi-square test.

2. The MITT population as reported in Table 3, there were 173 patients in the Ketorolac arm versus 82 in the vehicle arm. Based on the sensitivity analysis by classifying unreported outcomes as failures (i.e. SOIS>0) in both groups, the efficacy conclusions

did not change. The rates for Ketorolac and vehicle arms were 98/173(56.65%) and 21/82(25.61%) respectively; chi-square test's p-value:<0.0001.

### ***Sensitivity Analysis:***

For the ITT population, when missing SOIS were classified as failures (i.e., SOIS not equal to 0), patients receiving ketorolac 0.45% had a statistically significantly higher incidence of clearing of anterior chamber inflammation (SOIS = 0) compared to patients receiving vehicle at day 14 (98/176(55.7% vs. 21/87(24.1%; p-value < 0.001).

### **Secondary Analysis**

#### *Ocular Pain Resolution:*

There was a statistically significantly greater proportion of patients who were ocular pain-free at day 1 in the ketorolac 0.45% group, 70.0% (119/170 patients), compared to the vehicle group, 38.5% (30/78 patients) (p-value < 0.001).

#### *Inhibition of Surgically Induced Miosis:*

The mean pupil area measured post-I&A was not statistically significantly different between the two treatment groups (p-value = 0.413).

### **Efficacy Conclusions:**

In both studies, the efficacy data demonstrated that the new formulation of Ketorolac 0.45% was statistically significantly superior to vehicle in clearing of anterior chamber inflammation. In study 191578-005, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population, was 69/149(46.3%) in the ketorolac 0.45% arm versus 20/78(25.6%) in the vehicle arm (p-value=0.0025). In study 191578-006, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population, was 98/169(58.0%) in the ketorolac 0.45% arm versus 21/77(27.3%) in the vehicle arm (p-value<0.0001).

In addition, Ketorolac 0.45% demonstrated statistical significance to vehicle in one of the secondary endpoint of the resolution of ocular pain in both studies. The other secondary endpoint of mean pupil area measured post- irrigation and aspiration (I&A) failed to demonstrate statistical significance in both studies.



## **3.2 Evaluation of Safety**

### ***Safety Endpoints:***

In both studies, safety measurements were performed on days 1, 3, 7, and 14 and included assessments of adverse events, best-corrected visual acuity, biomicroscopy, and intraocular pressure. Dilated fundus examination in the operative eye was performed on day 14. The primary efficacy measurement, anterior segment inflammation assessment in the operative eye, was performed on days 1, 3, 7, and 14.

### ***Safety Analysis:***

In both studies, all safety analyses were based on the safety population. The incidence of ocular adverse events and other ocular variables were summarized on a per-eye basis for each treatment group. Non-ocular data were summarized on a per-patient (treatment regimen) basis. In the following a brief summary of adverse events is reported. See clinical review for further details.

### ***Study 191578-005:***

#### ***Adverse Events:***

The sponsor reported that no patients died during this study. Three patients experienced serious adverse events: 2 in the ketorolac 0.45% group (1.3% [2/157]) and 1 in the vehicle group (1.2% [1/81]). All of the serious adverse events were in the system organ class (SOC) cardiac disorders and were not considered related to treatment.

### ***Study 19157-06***

The sponsor reported that no patients died during this study. One patient experienced a serious adverse event: postprocedural haemorrhage (Investigator Term = post colonoscopy intestinal bleeding) experienced by a patient in the ketorolac 0.45% group.

#### 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor reported pooled data from both studies for the sub-group analyses. However, this reviewer has conducted subgroup analyses for individual studies separately. This reviewer has also conducted Breslow-Day test for treatment by subgroup interactions. Note that subgroup analyses are not powered for hypothesis testing, and there are multiple hypothesis testing problems. Thus, these subgroup analyses have to be interpreted carefully.

In the following we describe subgroup analyses by age-group, gender and race:

##### Study 191578 -005:

##### *Age-group:*

This reviewer has conducted Breslow-Day test for testing treatment by age-group (age  $\leq$  65 and age  $>$ 65) interaction. The test failed to detect the interaction (p-value= 0.9041). The proportion of patients with SOIS=0 is summarized in the following table:

**Table 8: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14 by Age-group**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Age $\leq$ 65	20/52 ( 38.46%)	6/31 (19.35%)	0.0695
Age $>$ 65	49/97 (50.52%)	14/47 (32.3%)	0.0187

It can be seen that from the above table that ketorolac 0.45% was statistically significantly superior to vehicle in the proportion of patients with a SOIS of 0 for the age group  $>$ 65. However, for the patients there in age-group  $\leq$  65, there is a numerical advantage of ketorolac 0.45% treated group over vehicle group.

##### *Gender:*

This reviewer has conducted Breslow-Day test for testing treatment by gender interaction. The test failed to detect the interaction (p-value= 0.2417). The proportion of patients with SOIS=0 is summarized in the following table:

**Table 9: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14 by Gender**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Male	24/63 (38.10%)	9/33(27.27%)	0.2890
Female	45/ 86 (52.33%)	11/ 45 (24.44%)	0.0022

It can be seen that from the above table that ketorolac 0.45% was statistically significantly superior to vehicle in the proportion of patients with a SOIS of 0 for the

female patients. However, for the male patients there is a numerical advantage of ketorolac 0.45% treated group over vehicle group.

**Race:**

This reviewer conducted Breslow-Day test for testing treatment by race (Caucasian and Non-Caucasian) interaction. The test has failed detected the interaction (p-value=0.6724). The proportion of patients with SOIS=0 is summarized in the following table:

**Table 10: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14 by Race**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Caucasian	65/136 ( 41.79%)	19/68 (27.94%)	0.0066
Non-Caucasian	4/ 13 ( 30.77%)	1/ 10 (10.00%)	0.2313

It can be seen that from the above table that ketorolac 0.45% was statistically significantly superior to vehicle in the proportion of patients with a SOIS of 0 for the Caucasian patients. For non-Caucasian patients, there is a numerical advantage of ketorolac 0.45% treated group over vehicle group.

**Study 191578 -006:**

**Age-group:**

This reviewer conducted Breslow-Day test for testing treatment by age-group (age ≤ 65 and age >65) interaction. The test failed to detect the interaction (p-value= 0.4679). The proportion of patients with SOIS=0 is summarized in the following table:

**Table 11: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14 by Age-group**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Age ≤ 65	27/55 ( 49.09%)	5/31 (16.13%)	0.0024
Age >65	71/114 (62.28%)	16/46 (34.78%)	0.0016

It can be seen that from the above table that ketorolac 0.45% was statistically significantly superior to vehicle in the proportion of patients with a SOIS of 0 for either age-group.

**Gender:**

This reviewer conducted Breslow-Day test for testing treatment by gender interaction. The test failed to detect the interaction (p-value= 0.4681). The proportion of patients with SOIS=0 is summarized in the following table:

**Table 12: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14 by Gender**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Male	37/72 ( 51.39%)	5/30 (16.67%)	0.0012
Female	61/ 97 ( 62.89%)	16/ 47 (34.04%)	0.0011

It can be seen that from the above table that ketorolac 0.45% was statistically significantly superior to vehicle in the proportion of patients with a SOIS of 0 for either gender.

***Race:***

This reviewer conducted Breslow-Day test for testing treatment by race (Caucasian and Non-Caucasian) interaction. The test has detected the interaction (p-value=0.0097). The proportion of patients with SOIS=0 is summarized in the following table:

**Table 13: Clearing of Anterior Chamber Inflammation: SOIS Equal to 0 (Modified Intent-to-Treat Population with LOCF) at Day 14 by Age-group**

Day 14	Ketorolac 0.45%	Vehicle	P-value (Chi-square)
Caucasian	77/140 ( 55.00%)	20/62 (32.26%)	0.0028
Non-Caucasian	21/ 29 ( 72.41%)	1/ 15 (6.67%)	<0.0001

It can be seen that from the above table that ketorolac 0.45% was statistically significantly superior to vehicle in the proportion of patients with a SOIS of 0 for Caucasian and non-Caucasian patients.

Note that the presence of interaction indicates that the treatment benefit is different in the two subgroups. Although there is differential effect for the treatment due to race, it is going in the same direction demonstrating statistical significance of superiority for ketorolac 0.45% over vehicle for the primary endpoint. However, because of small sample size in Non-Caucasian patient group, the interpretation of interaction effect has limitations.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

Last observation carried forward (LOCF) was used for imputing missing values. There are concerns in using LOCF which can potentially bias the results. Furthermore, the sponsor did not include all the mITT patients in the mITT-LOCF analysis. According to sponsor, no imputation could be done for missing data on day 1 and hence this reviewer performed sensitivity analysis by classifying the missing values as failures for those patients who were not included in the sponsor's mITT-LOCF analysis.

In study 191578-005, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population, was 69/149(46.3%) in the ketorolac 0.45% arm versus 20/78(25.6%) in the vehicle arm (p-value=0.0025). The MITT population as reported in Table 2, there were 155 patients in the Ketorolac arm versus 79 patients in the vehicle arm. This reviewer has conducted a sensitivity analysis by classifying unreported patients' outcomes as failures (i.e. SOIS>0) in both groups. The efficacy conclusions did not change based on the sensitivity analysis (69/155(44.52%) for Ketorolac0.45% versus 20/79(25.32%) for the vehicle; chi-square test's p-value:0.0042.

In study 191578-006, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population, was 98/169(58.0%) in the ketorolac 0.45% arm versus 21/77(27.3%) in the vehicle arm (p-value<0.0001). The MITT population as reported in Table 3, there were 173 patients in the Ketorolac arm versus 82 in the vehicle arm. Based on the sensitivity analysis by classifying unreported outcomes as failures (i.e. SOIS>0) in both groups, the efficacy conclusions did not change. The rates for Ketorolac and vehicle arms were 98/173(56.65%) and 21/82(25.61%) respectively; chi-square test's p-value:<0.0001.

The interaction effect was also evaluated between treatment by subgroups such as gender, race and age. The Breslow and Day test has not detected any significant interaction between treatment by subgroups for study 191578-005. However, in study 191578-006, The Breslow and Day test has detected interaction effect (p-value=0.0097) between treatment by race subgroup (Caucasian vs. non-Caucasian). Note that the presence of interaction indicates that the treatment benefit is different in the two subgroups. Although there is differential effect for the treatment due to race, it is going in the same direction demonstrating statistical significance of superiority for ketorolac 0.45% over vehicle for the primary endpoint. However, because of small sample size in Non-Caucasian patient group, the interpretation of interaction effect has limitations.

## 5.2 Conclusions and Recommendations

In both studies, the efficacy data demonstrated that the new formulation of Ketorolac 0.45% was statistically significantly superior to vehicle in clearing of anterior chamber inflammation. In study 191578-005, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population was 69/149(46.3%) in the ketorolac 0.45% arm versus 20/78(25.6%) in the vehicle arm (p-value=0.0025). In study 191578-006, the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) at day 14 after cataract surgery in the mITT population was 98/169(58.0%) in the ketorolac 0.45% arm versus 21/77(27.3%) in the vehicle arm (p-value<0.0001).

In addition, Ketorolac 0.45% demonstrated statistical significance to vehicle in one of the secondary endpoint of the resolution of ocular pain in both studies. The other secondary endpoint of mean pupil area measured post- irrigation and aspiration (I&A) failed to demonstrate statistical significance in both studies.

According to sponsor's reporting of safety issues, patients receiving ketorolac 0.45% had a lower incidence of ocular adverse events than patients receiving vehicle in both studies. More details on safety can be obtained from the clinical review.

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