CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-528

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21528
Name of drug:	Ketorolac (Ketorolac Tromethamine Ophthalmic Solution 0.4%)
Applicant:	Allergan
Indication:	Relief of Pain in Post-Operative Unilateral Photorefractive Keratectomy Patients
Documents reviewed:	Statistical Section of Electronic NDA Submission (pathway: \\CDSESUB1\N21528\N_000\2002-08-06\clinstat)
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Keywords: NDA review, clinical studies, categorical data analysis

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1. Executive Summary of Statistical Findings

1.1. Overview of Clinical Program and Studies Reviewed

NDA-21528 (ketorolac tromethamine ophthalmic solution 0.4%) was submitted for the indication of pain relief in post-operative unilateral photorefractive keratectomy (PRK) patients. Two identically designed phase III studies (191578-002 and 191578-003) were submitted to support the indication. A total of 313 patients was studied in the two phase III studies (156 in Study 191578-002 and 157 in Study 191578-003).

1.2. Principal Findings and Conclusions

Ketorolac has demonstarted superiority to Vehicle in terms of maximum pain intensity during the first 12 hour period post PRK surgery in both Studies 191578-002 and 191578-003. The results for the primary finding is presented in Tables 1 and 2 below. The superiority of Ketorolac is also supported by secondary findings in maximum pain intensity during the subsequent 12 hour periods post PRK surgery, first time to no pain, pain relief, use of escape medication, severity of ocular symptoms and the results of subgroup analyses requested by FDA (excluding center 3753 in Study 191578-002 and excluding center 3508 in Study 191578-003).

Table 1. Maximum Pain Intensity during 1st 12-Hour Period

	Ketorolac N = 77 n (%)	Vehicle N = 79 n (%)	P-value
Pain Intensity Category			
N	75[a]	77[b]	p < 0.001[c]
No Pain	10 (13.3%)	1 (1.3%)	
Mild Pain	19 (25.3%)	2 (2.6%)	
Moderate Pain	16 (21.3%)	11 (14.3%)	
Severe Pain	25 (33.3%)	46 (59.7%)	
Intolerable Pain	5 (6.7%)	17 (22.1%)	
Pain Intensity Scores			
Median	2.0	3.0	
Mean	1.9	3.0	
SD	1.18	0.77	

a: Patient 3379-1066 and Patient 3751-1020 were missing from this analysis as pain intensity was not recorded during the 1st 12-hour post-PRK surgery period.
b: Patients 3753-1097 and Patient 3751-1130 were missing from this analysis. Patient 3753-1097 exited study after receiving study medication and Patient 3751-1130 did not have pain intensity recorded during the 1st 12-hour post-PRK surgery period.
c: P-values calculated from CMH test for row mean score differences with modified ridits, stratified by investigator.

Table 2. Maximum Pain Intensity during 1st 12-Hour Period

	Ketorolac N = 79 n (%)	Vehicle N = 78 n (%)	P-value
Pain Intensity Category			
N	79	78	p < 0.001[a]
No Pain	9 (11.4%)	0 (0.0%)	

Mild Pain	25 (31.6%)	3 (3.8%)
Moderate Pain	11 (13.9%)	7 (9.0%)
Severe Pain	27 (34 2%)	52 (66 7)
Intolerable Pain	7 (8 9%)	16 (20 5%)
Pain Intensity Scores		
Median	2 0	3 0
Mean	2 0	3 0
SD	1.22	0.67

a·P-values calculated from CMH test for row mean score differences with modified ridits, stratified by investigator.

2. Statistical Review and Evaluation of Evidence

2.1. Introduction and Background

NDA-21528 (ketorolac tromethamine ophthalmic solution 0.4%) was submitted for the indication of pain relief in post-operative unilateral photorefractive keratectomy (PRK) patients. Two identically designed phase III studies (191578-002 and 191578-003) were submitted to support the indication A total of 313 patients was studied in the two phase III studies (156 in Study 191578-002 and 157 in Study 191578-003).

2.2. Data Analyzed and Sources

The dataset analyzed by this reviewer was pain.xpt submitted by the sponsor in electronic document room with pathway '\\CDSESUB1\N21528\N_000\2002-08-06\crt\datasets\002analysis' and '\CDSESUB1\N21528\N_000\2002-08-06\crt\datasets\003analysis'.

2.3 Statistical Evaluation of Evidence on Efficacy

2.3.1. Protocol (Study 191578-002 and Study 191578-003)

This was a multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. The primary objective of this study was to evaluate the safety and analgesic efficacy of ketorolac tromethamine ophthalmic solution 0.4% in post-operative unilateral photorefractive keratectomy (PRK) patients.

Patients received study treatment for up to 4 days. Screening procedures were performed at visit 1 (day −7 through day -1). At visit 2 (day 0), patients underwent PRK surgery, followed immediately by administration of 1 drop of the masked study treatment into the study eye. Patients then self-administered 1 drop of study medication in the study eye approximately 3 hours post-operatively, and then every 4 hours while awake on visit 2 (day 0) (up to a total of 4 doses). On visits 3 through 5 (days 1 through 3), patients self-administered the masked study treatment 4 times daily. [redacted] was administered to the study eye approximately 5 minutes prior to each dose of masked study treatment on visits 2 through 5 (days 0 to 3). Escape medication [redacted]) was to be administered as needed for intolerable pain during the treatment period. During the treatment period, patients recorded, in electronic patient diaries, current pain intensity immediately prior to each dose of [redacted] and escape medication, and pain relief

(from the last dose of masked study treatment) approximately 2 hours after each dose of masked study treatment (except during the immediate post-operative period).

Pain intensity was scored on a 5–point scale with 0 = no pain to 4 = intolerable pain. Pain intensity was analyzed in 12-hour periods post-PRK surgery. For each patient, the 12-hour post PRK surgery period was represented by the maximum pain intensity score recorded during the period. The primary efficacy endpoint in this study was pain intensity during the 1st 12-hour post-PRK surgery period. Secondary efficacy endpoints included maximum pain intensity in all subsequent 12-hour periods (through visit 5, day 3), time to zero pain intensity, pain relief. Other efficacy endpoints included use of escape medication and severity of ocular symptoms (foreign body sensation, photophobia, burning/stinging, tearing, and itching with 5-point severity scale).

Maximum pain intensity in the first 12 hours was analyzed in ITT (all randomized patients) population in the following manner.

- For each patient, the first 12-hour post PRK period was represented by the maximum pain intensity score recorded during the period, which was either prior to taking the masked medication or escape medication, excluding the hour 0 assessment.
- If a patient did not have any pain intensity ratings recorded during the first 12-hour period post-PRK, then no data imputation was performed.
- Two-way ANOVA model including the main effects of treatment and center was used to test treatment difference between ketorolac and vehicle with a two sided significance level of 0.05. If the assumptions for normality are not met then the null hypothesis will be tested using the Cochran-Mantel-Haenszel (CMH) test stratified by investigator, using modified ridit scores and testing for row mean score.

Maximum pain intensity in the first 12 hours was also analyzed in the modified ITT population (patients who did not violate protocol entrance or study criteria) and per protocol population (patients who did not violate protocol entrance or study criteria and did not use escape medication). Maximum pain intensity in the second and subsequent 12-hour periods post-PRK were analyzed similarly. Time (hours) to zero pain intensity were examined using the generalized Wilcoxon rank sum test from a survival analysis using the ITT population. Kaplan-Meier curves were provided.

Pain relief ratings, which will also be recorded on the electronic diary up to day 3, approximately two hours after each instillation of masked study treatment (except during the immediate post-operative period), will document the amount of pain relief in the study eye achieved by the previous dose of masked study treatment. Pain relief will be collected on a 0 (I received complete pain relief) to 4 (I received no pain relief) scale. Pain relief in 12-hour periods using the ITT, PP, and MITT populations was analyzed similarly to pain intensity that if a patient had more than 1 pain relief rating during any post-PRK analysis period, then the maximum (i.e., worst response) of these observed ratings was used. Binomial response categories of escape medication taken/not taken during each 12-hour period post-PRK using the ITT population were compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test (Mantel and Haenszel, 1959) for general association, stratified by investigator. In addition, the treatment-by-investigator interaction were examined statistically by performing the Breslow-Day (BD) test (Breslow and Day, 1980) with a significance level of 0.10. The total number of tablets of relief medication taken by a patient were compared between groups in the same

manner as for the primary efficacy analysis. In addition, time to first use of escape medication were examined using the generalized Wilcoxon rank sum test from a survival analysis. Kaplan-Meier curves were provided. Differences in ocular symptoms between treatment groups and test for interaction were analyzed with a 2-way ANOVA model by symptom, in the same manner as for the primary efficacy analysis using the ITT, PP, and MITT populations.

A sample size of 63 was proposed for each treatment group. With this sample size and the assumptions given for treatment difference and standard deviation, Table 3 presents the power of this study.

Table 3. Power of Study with a Sample Size of 63/Treatment

Standard Deviation	Delta (grade difference to detect)		
	0.5	0.7	0 9
1 00	79%	97%	99%
1 12	70%	93%	99%
1.25	60%	87%	97%

2.3.2. Sponsor's Results

2.3.2.1 Study 191578-002

2.3.2.1.1 Patient Disposition

The intent-to-treat (ITT) population included all patients randomized: 77 patients to Ketorolac and 79 patients to Vehicle. The detailed patient disposition is presented in Table 4 below.

Table 4. Patient Disposition

Exit Status	Keto (N=77)	Vehicle (N=79)	Total (N=156)
Total Randomized	77	79	156
Total Completed	72 (93 5%)	75 (94.9%)	147 (94.2%)
Total Discontinued	5 (6.5%)	4 (5.1%)	9 (5.8%)
Reasons for Discontinuation			
Adverse Event	5 (6.5%)	2 (2.5%)	7 (4.5%)
Administrative Reasons			
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inability to Continue	0 (0.0%)	1 (1.3%)	1 (0 6%)
Patient/Parent/LAR choice	0 (0.0%)	0 (0.0%)	0 (0 0%)
Protocol Violations			
Improper Entry	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Compliance	0 (0.0%)	1 (1.3%)	1 (0.6%)
Concomitant Therapy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Terminated	0 (0.0%)	0 (0.0%)	0 (0.0%)

2.3.2.1.2. Demographics

The treatment groups in the ITT population were similar in demographic characteristics. Overall, the mean age was 39.9 years (range 18 to 66 years). There were more males (55 8%, 87/156) than females (44.2%, 69/156). The population was primarily Caucasian (84.0%, 131/156), with 7.1% (11/156) black and 5.1% (8/156) Hispanic. The most common iris colors were brown (42 3%, 66/156) and blue (35.3%, 55/156). Detailed information for patient demographics is included in Table 5 below.

Table 5. Patient Demographics

		Keto (N=77)	Vehicle (N=79)	Total (N=156)
Age (Years)	N	77	79	156
	Mean	40.4	39 4	39.9
	SD	10.69	10.64	10.64
	Median	38.0	38.0	38.0
	Min	18	23	18
	Max	66	64	66
Sex	N	77	79	156
	Male	40 (51.9%)	47 (59.5%)	87 (55.8%)
	Female	37 (48.1%)	32 (40.5%)	69 (44 2%)
Race	N	77	79	156
	Caucasian	64 (83.1%)	67 (84.8%)	131 (84.0%)
	Black	3 (3.9%)	8 (10.1%)	11 (7.1%)
	Asian	4 (5.2%)	2 (2.5%)	6 (3 8%)
	Hispanic	6 (7.8%)	2 (2 5%)	8 (5.1%)
Eye Color	N	77	79	156
	Blue	32 (41.6%)	23 (29 1%)	55 (35.3%)
	Brown	29 (37.7%)	37 (46.8%)	66 (42.3%)
	Green	5 (6.5%)	6 (7 6%)	11 (7.1%)
	Hazel	10 (13.0%)	13 (16.5%)	23 (14.7%)

Pain intensity was recorded prior to the first dose of study medication (i.e., recorded immediately after surgery and prior to the first dose of study medication). Only 98 out of 157 patients had baseline pain intensity scores available The mean pain intensity score was 0.5 in the Ketorolac group and 0.4 in the Vehicle group. There were no meaningful differences between the treatment groups in the distribution of patients in the different pain intensity categories. The results for baseline pain intensity is presented in Table 6 below.

Table 6. Baseline Pain Intensity

Severity Category and Descriptive Statistics	Keto (N=77)	Vehicle (N=79)	Total (N=156)
No pain	30 (61.2%)	37 (75.5%)	67 (68.4%)
Mild Pain	14 (28.6%)	7 (14.3%)	21 (21.4%)
Moderate pain	4 (8.2%)	2 (4.1%)	6 (6.1%)
Severe pain	1 (2.0%)	3 (6.1%)	4 (4.1%)
Intolerable pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
N	49	49	98
Mean	0.5	0.4	0.5
SD	0.74	0.84	0.79
Median	0	0	0
Min	0	0	0
Max	3	3	3

2.3.2.1.3. Efficacy Results

The results reported in this section are based on ITT population. Results in PP and MITT populations are consistent with those in ITT population.

Primary Endpoint

Maxim Pain Intensity during 1st 12-Hour Period

The median of maximum pain intensity score during the 1st 12-hour post-surgery period was 1.0 unit lower in the Ketorolac group compared to the Vehicle group with a median score of 2.0 in the Ketorolac group and 3.0 in the Vehicle group. There was a significant difference in the distribution of patients in the different pain intensity categories in favor of the Ketorolac group ($p < 0.001$). There were fewer patients in the 'severe pain' to 'intolerable pain' categories in the Ketorolac group (40.0%, 30/75) compared to the Vehicle group (82.0%, 63/77). Detailed Results for the maximum pain intensity during the 1st 12-hour period is presented in Table 7 below.

Table 7. Maximum Pain Intensity during 1st 12-Hour Period

	Ketorolac N = 77 n (%)	Vehicle N = 79 n (%)	P-value
Pain Intensity Category			
N	75[a]	77[b]	p < 0.001[c]
No Pain	10 (13.3%)	1 (1.3%)	
Mild Pain	19 (25.3%)	2 (2.6%)	
Moderate Pain	16 (21.3%)	11 (14.3%)	
Severe Pain	25 (33.3%)	46 (59.7%)	
Intolerable Pain	5 (6.7%)	17 (22.1%)	
Pain Intensity Scores			
Median	2.0	3.0	
Mean	1.9	3.0	
SD	1.18	0.77	

a: Patient 3379-1066 and Patient 3751-1020 were missing from this analysis as pain intensity was not recorded during the 1st 12-hour post-PRK surgery period.
b: Patients 3753-1097 and Patient 3751-1130 were missing from this analysis. Patient 3753-1097 exited study after receiving study medication and Patient 3751-1130 did not have pain intensity recorded during the 1st 12-hour post-PRK surgery period.
c: P-values calculated from CMH test for row mean score differences with modified ridits, stratified by investigator

Secondary Endpoints

Maximum Pain Intensity in Later 12-Hour Periods

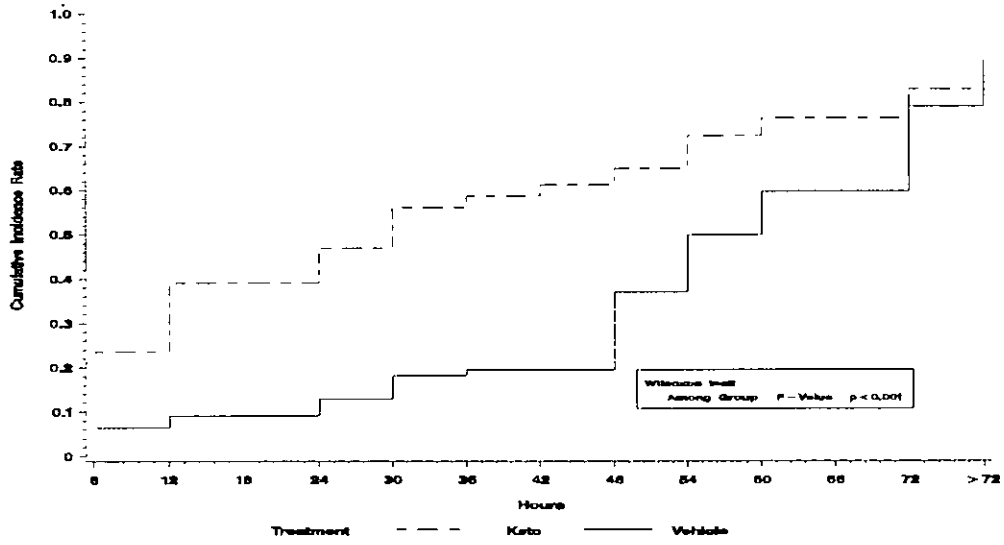
The median of maximum pain intensity scores during the 2nd and 3rd 12-hour post-PRK surgery periods (ie, 12 to 24 hours and 24 to 36 hours) were lower in the Ketorolac group (1.0 and 1.0) compared to the Vehicle group (3.0 and 3.0). There was a significant difference in the distribution of patients in the different pain intensity categories during the 2nd and 3rd 12-hour post-PRK surgery periods in favor of the Ketorolac group ($p < 0.001$). There were fewer patients in the 'severe' to 'intolerable pain' categories in the Ketorolac group (27.6% [21/76] and 28.6% [22/77], respectively) compared to the Vehicle group (51.9% [40/77] and 59.0% [46/78], respectively). There were no

significant differences between the treatment groups in pain intensity recorded during the remaining 12-hour periods (p =0.183).

Time to First No Pain

Using the Wilcoxon rank sum test from a survival analysis, there was a significant difference in cumulative incidence rates of time to first no pain in favor of the Ketorolac group (p<0.001). The median time to first no pain was achieved by 30 hours in the Ketorolac group compared to 54 hours in the Vehicle group. During the 1st 12-hour post-PRK surgery period, 39.0% of patients in the Ketorolac group achieved no pain, compared to 8.9% of patients in the Vehicle group. Kaplan-Meier estimate of first no pain is presented in Figure 1 below.

Figure 1. Kaplan-Meier Estimator for Accumulated Incidence Rate of First No Pain



Pain Relief

The Ketorolac group had greater pain relief than the Vehicle group during the 1st 12-hour post-PRK surgery period, with a median pain relief score of 3.0 compared to 4.0 in the Vehicle group. There was a significant difference in the distribution of patients in the different pain relief categories in favor of the Ketorolac group (p =0.001). There were fewer patients in the 'little' and 'no pain relief' categories in the Ketorolac group (40.3%, 29/72) compared to the Vehicle group (82.9%, 63/76). Results for pain relief at the 1st 12 hour period is presented in Table 8 below.

Table 8. Maximum Pain Relief during 1st 12-Hour Period

Severity Category and Descriptive Statistics	Keto (N=77)	Vehicle (N=79)	Treatment P-value[a]
Complete pain relief	9 (12.5%)	1 (1.3%)	<0.001
Great deal pain relief	10 (13.9%)	1 (1.3%)	
Fair amount pain relief	24 (33.3%)	11 (14.5%)	

Little pain relief	19 (26 4%)	30 (39.5%)
No pain relief	10 (13 9%)	33 (43.4%)
N	72	76
Mean	3 2	4.2
SD	1 21	0.84
Median	3 0	4 0
Min	1	1
Max	5	5

[a] P-values are from CMH test for row mean score differences with modified ridits, stratified by investigator

Pain relief was also greater in the Ketorolac group during the 2nd to 5th 12-hour post-PRK surgery periods (ie, 12 to 24 hours, 24 to 36 hours, 36 to 48 hours, and 48 to 60 hours). The median pain relief scores during the 2nd to 5th 12-hour post-PRK surgery periods were lower in the Ketorolac group (3 0, 3.0, 3.0, and 3.0, respectively) compared to the Vehicle group (4.0, 4.0, 4.0, and 4 0, respectively) There was a significant difference in the distribution of patients in the different pain relief categories during the 2 nd to 5 th 12-hour post-PRK surgery periods in favor of the Ketorolac group (p =0.043). There were fewer patients in the 'little' and 'no pain relief' categories in the Ketorolac group (36.5% [27/74]; 41.5% [32/77]; 42.9% [33/77]; and 44.2% [34/77], respectively) compared to the Vehicle group (61.0% [47/77], 74.4% [58/78], 53.8% [42/78]; 52.6% [41/78], respectively). There were no significant differences between the treatment groups in pain relief recorded during the remaining 12-hour periods (p =0.076).

Use of Escape Medication

During the 1st 12-hour post-PRK surgery period, significantly fewer patients in the Ketorolac group (44.2%, 34/77) took escape medication compared to the Vehicle group (88.5%, 69/78; p < 0.001). Use of escape medication was also significantly lower during the 2nd and 3rd 12-hour post-PRK surgery periods in the Ketorolac group (26.0%[20/77] and 26% [20/77], respectively) compared to the Vehicle group (62.8% [49/78] and 60.3%, [47/78], respectively; p < 0.001). There were no significant differences in the use of escape medication for the subsequent 12-hour periods (p =0.250).

The number of patients using escape medication ( ) per 12-hour post-PRK surgery periods is summarized in Table 9 below.

Table 9. Number of Patients Using Escape Medication

12-Hour Periods Post-Surgery	Ketorolac N = 77 n (%)	Vehicle N = 79 n (%)	P-value[a]
N[b]	77	78[c]	
1st 12-hour (0 to 12)	34 (44 2%)	69 (88.5%)	p < 0 001
2nd 12-hour (12 to 24)	20 (26 0%)	49 (62.8%)	p < 0.001
3rd 12-hour (24 to 36)	20 (26 0%)	47 (60.3%)	p < 0.001
4th 12-hour (36 to 48)	15 (19 5%)	21 (26.9%)	0.250
5th 12-hour (48 to 60)	14 (18.2%)	17 (21.8%)	0.528
6th 12-hour (60 to 72)	6 (7 8%)	4 (5.1%)	0.570
7th 12-hour (72-84)	1 (1 3%)	0 (0.0%)	0.333

a P-values calculated from CMH test for general association using table scores, stratified by investigator.
b If a patient did not record use of escape medication during a 12-hour post-PRK surgery period, then 'no use' was imputed for that period Thus the N remained constant over the 12-hour post-PRK surgery periods.
c Patient 3753-1097 was missing all follow-up data, no data were imputed.

During the 1st 12-hour post-PRK surgery period, fewer tablets of escape medication were used in the Ketorolac group (median = 0.0 tablets) compared to the Vehicle group (median = 2.0 tablets). There was a significant difference in the distribution of the number of tablets of escape medication used by patients in favor of the Ketorolac group ($p < 0.001$). Fewer patients in the Ketorolac group (10.4%, 8/77) reported using 3 tablets or more compared to the Vehicle group (48.7%, 38/78). The total number of tablets taken during the 1st 12-hour period was summarized in Table 10 below.

Table 10. Total Number of Tablets Taken during the 1st 12-Hour Period

Number of Tablets and Descriptive Statistics	Keto (N=77)	Vehicle (N=79)	Treatment P-value[a]
None	43 (55 8%)	9 (11.5%)	<0.001
1 tablet	14 (18 2%)	15 (19 2%)	
2 tablets	12 (15.6%)	16 (20.5%)	
3 tablets	8 (10 4%)	26 (33.3%)	
4 o r more tablet	0 (0.0)	12 (15.4%)	
N	77	78	
Mean	0.8	2.3	
SD	1 05	1 42	
Median	0 0	2 0	
Min	0	0	
Max	3	7	

(a) P-values are from CMH test for row mean score differences with modified ridits, stratified by investigator.

The median number of tablets used during the 2nd and 3rd 12-hour post-PRK surgery periods (i.e., 12 to 24 hours, and 24 to 36 hours) was lower in the Ketorolac group (0.0 and 0.0 tablets, respectively) compared to the Vehicle group (1.0 and 1.0 tablets, respectively). There was a significant difference in the distribution of the number of tablets of escape medication used by patients in favor of the Ketorolac group ($p < 0.001$). Fewer patients in the ketorolac group (1.3% [1/77] and 3.9% [3/77], respectively) reported using 3 tablets or more compared to the Vehicle group (6.4% [5/78] and 14.1% [11/78], respectively). There were no significant differences between treatment groups in the number of tablets of escape medication used in the remaining 12-hour post-PRK surgery periods

Using the Wilcoxon rank sum test from a survival analysis, there was a significant difference in cumulative incidence rates of time to first use of escape medication in favor of the Ketorolac group ($p < 0.001$). The median time to 1st use of escape medication occurred by 18 hours in the Ketorolac group, compared to within the 1st 6 hours in the Vehicle group. The first use of escape medication occurred within the 1st 12-hour post-PRK surgery period for 44 2% of patients in the Ketorolac group compared to 87.9% of patients in the Vehicle group. The Kaplan-Meier estimator for cumulative incidence rates of first use of escape medication is presented in Figure a.1 in Appendix A.

Ocular Symptom

At day 1 (approximately 24 hours post-PRK surgery), for the ocular symptoms foreign body sensation, photophobia, burning/stinging, and tearing, there was a significant difference in the distribution of patients in the different ocular symptom severity category in favor of the Ketorolac group ($p \leq 0.018$). There were no significant differences between treatment groups for these ocular symptoms at the other visits ($p \geq 0.076$). For the ocular

symptom, itching, there were no significant differences between treatment groups at any of the visits during the treatment period (p =0.585).

2 3.2.1.4. Results across Centers and Subgroups

There were no significant treatment-by-center interactions in the analyses of pain intensity and pain relief. There was a significant treatment-by-center interaction in the analysis of escape medication during the 1st 12-hour post-PRK surgery period (p = 0.002) For investigator 3751, similar proportions (around 70%) of patients in both Ketorolac and Vehicle treatment groups reported use of escape medication in the 1st 12-hour period post-PRK (11/16 (69%) in Ketorolac group and 10/15 (67%) in Vehicle group). For all other investigators, a much larger proportion of patients in the Vehicle treatment group reported use of escape medication in the 1st 12-hour post-PRK surgery period. Therefore, the interaction was not judged as qualitative.

As per FDA's request, subgroup efficacy analysis was performed after excluding patients from study site # 3753 to determine the effect of this center's data on the results of the study. The results of the analyses of the primary, as well as secondary efficacy variables excluding data from study site # 3753 were similar to those obtained in the analyses including data from this site, indicating no significant impact of this site's data on the overall results of the study.

2.3.2.2. Study 191578-003

2.3.2.2.1. Patient Disposition

The intent-to-treat (ITT) population included all patients randomized: 79 patients to Ketorolac and 78 patients to Vehicle. The detailed patient disposition is presented in Table 11 below.

Table 11. Patient Disposition

Exit Status	Keto (N=79)	Vehicle (N=78)	Total (N=157)
Total Randomized	79	78	157
Total Completed	78 (98.7%)	69 (88.5%)	147 (93.6%)
Total Discontinued	1 (1.3%)	9 (11.5%)	10 (6 4%)
Reasons for Discontinuation			
Adverse Event	1 (1.3%)	6 (7.7%)	7 (4.5%)
Administrative Reasons			
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inability to Continue	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient/Parent/LAR choice	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Violations			
Improper Entry	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Compliance	0 (0.0%)	1 (1.3%)	1 (0.6%)
Concomitant Therapy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	2 (2.6%)	2 (1.3%)
Study Terminated	0 (0.0%)	0 (0.0%)	0 (0.0%)

2.3.2.2.2. Demographics

The treatment groups in the ITT population were similar in demographic characteristics. Overall, the mean age was 38.9 years (range 20 to 66 years). There were more females (58.0%, 91/157) than males (42 0%, 66/157). The population was primarily Caucasian (94 3%, 148/157), with 3.2% (5/157) black. The most common iris colors were brown (33 1%, 52/157) and blue (31.2%, 49/157). Detailed information for patient demographics is included in Table 12 below.

Table 12. Patient Demographics

		Keto (N=79)	Vehicle (N=78)	Total (N=157)
Age (Years)	N	79	78	157
	Mean	39 2	38.6	38.9
	SD	10.11	9 18	9.63
	Median	39.0	38.0	38.0
	Min	21	20	20
	Max	66	56	66
Sex	N	79	78	157
	Male	29 (36.7%)	37 (47.4%)	66 (42 0%)
	Female	50 (63.3%)	41 (52.6%)	91 (58.0%)
Race	N	79	78	157
	Caucasian	73 (92.4%)	75 (96.2%)	148(94.3%)
	Black	3 (3.8%)	2 (2.6%)	5 (3.2%)
	Asian	1 (1.3%)	0 (0.0)	1 (0.6%)
	Hispanic	1 (1.3%)	1 (1.3%)	2 (1.3%)
	Other[b]	1 (1.3%)	0 (0.0)	1 (0.6%)
Eye Color	N	79	78	157
	Blue	23 (29 1%)	26 (33.3%)	49 (31.2%)
	Brown	29 (36.7%)	23 (29.5%)	52 (33.1%)
	Green	12 (15.2%)	11 (14.1%)	23 (14.6%)
	Hazel	15 (19.0%)	18 (23.1%)	33 (21.0%)
	Other	0 (0.0)	0 (0.0)	0 (0.0)

Pain intensity was recorded prior to the first dose of study medication (i.e., recorded immediately after surgery and prior to the first dose of study medication). Only 138 out of 157 patients had baseline pain intensity scores available. The mean pain intensity score was 0.1 in both the Ketorolac and the Vehicle groups, reflecting the persistence of the operative anesthetic. There were no meaningful differences between the treatment groups in the distribution of patients in the different pain intensity categories. Results for baseline pain intensity is presented in Table 13 below.

Table 13. Baseline Pain Intensity

Severity Category and Descriptive Statistics	Keto (N=79)	Vehicle (N=78)	Total (N=157)
No pain	67 (94.4%)	63 (94.0%)	130 (94.2%)
Mild Pain	3 (4.2%)	4 (6.0%)	7 (5.1%)
Moderate pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intolerable pain	1 (1.4%)	0 (0.0%)	1 (0.7%)
N	71	67	138
Mean	0.1	0.1	0.1
SD	0.51	0.24	0.40

Median	0	0	0
Min	0	0	0
Max	4	1	4

2.3.2.2.3. Efficacy Results

The results reported in this section are based on ITT population. Results in PP and MITT populations are consistent with those in ITT population.

Primary Endpoint

Maxim Pain Intensity during 1st 12-Hour Period

The median pain intensity score during the 1st 12-hour post-surgery period was 1.0 unit lower in the Ketorolac group compared to the Vehicle group with a median score of 2.0 in the Ketorolac group and 3.0 in the Vehicle group. There was a significant difference in the distribution of patients in the different pain intensity categories in favor of the Ketorolac group ($p < 0.001$) There were fewer patients in the 'severe pain' to 'intolerable pain' categories in the Ketorolac group (43 0%, 34/79) compared to the Vehicle group (87.2%, 68/78).Detailed Results for the maximum pain intensity during the 1st 12-hour period is presented in Table 14 below.

Table 14. Maximum Pain Intensity during 1st 12-Hour Period

	Ketorolac N = 79 n (%)	Vehicle N = 78 n (%)	P-value
Pain Intensity Category			
N	79	78	p < 0 001[a]
No Pain	9 (11 4%)	0 (0.0%)	
Mild Pain	25 (31.6%)	3 (3 8%)	
Moderate Pain	11 (13.9%)	7 (9 0%)	
Severe Pain	27 (34 2%)	52 (66.7)	
Intolerable Pain	7 (8 9%)	16 (20.5%)	
Pain Intensity Scores			
Median	2.0	3.0	
Mean	2 0	3 0	
SD	1 22	0 67	

a P-values calculated from CMH test for row mean score differences with modified ridits, stratified by investigator.

Secondary Endpoints

Maximum Pain Intensity in Later 12-Hour Periods

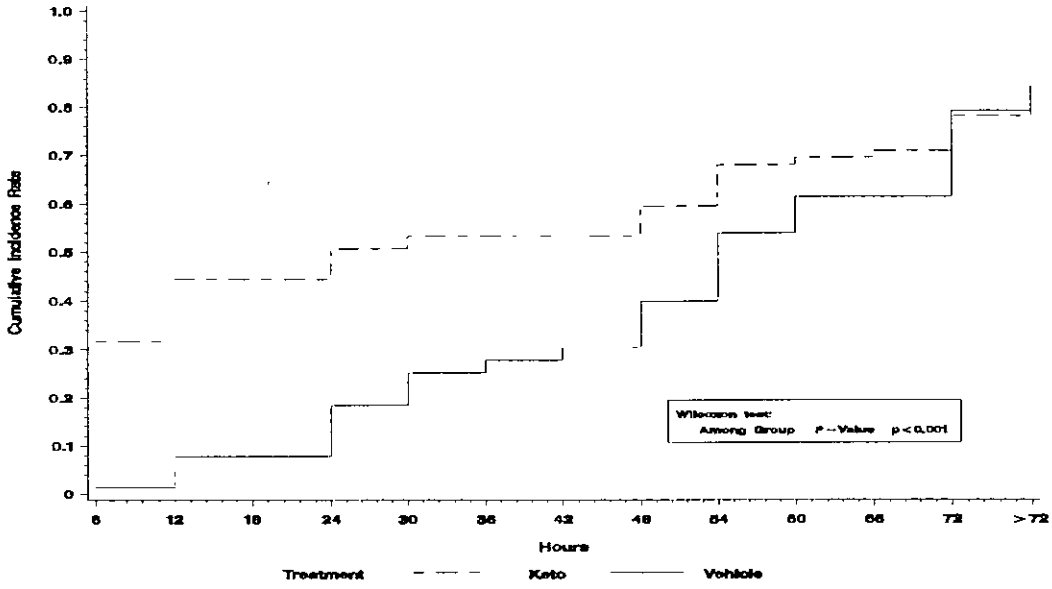
The median pain intensity scores during the 2nd, 3rd, and 4th 12-hour post-PRK surgery periods (ie, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours) were lower in the Ketorolac group (2.0, 2.0, and 2.0, respectively) compared to the Vehicle group (3.0, 3.0, and 3.0, respectively). There was a significant difference in the distribution of patients in the different pain intensity categories during the 2nd, 3rd, and 4th 12-hour post-PRK surgery periods in favor of the Ketorolac group ($p \leq 0.001$). There were fewer patients in the 'severe' to 'intolerable pain' categories in the Ketorolac group (45.6% [36/79]; 36.7%

[29/79]; and 35.4% [28/79], respectively) compared to the Vehicle group (73.1% [57/78]; 70.5% [55/78]; and 61.5% [48/78], respectively). There were no significant differences between the treatment groups in pain intensity recorded during the remaining 12-hour periods ($p \geq 0.518$).

Time to First No Pain

Using the Wilcoxon rank sum test from a survival analysis, there was a significant difference in cumulative incidence rates of time to first no pain in favor of the Ketorolac group ($p < 0.001$). The median time to first no pain was achieved by 24 hours in the Ketorolac group compared to 54 hours in the Vehicle group. Time to first no pain was achieved during the 1st 12-hour post-PRK surgery period by 44.3% of patients in the Ketorolac group, compared to 7.8% of patients in the Vehicle group. The Kaplan-Meier Estimator for cumulative incidence rates of first no pain is presented in Figure 2 below.

Figure 2. Kaplan-Meier Estimator for Accumulated Incidence Rate of First No Pain



Pain Relief

The Ketorolac group had greater pain relief than the Vehicle group during the 1st 12-hour post-PRK surgery period, with a median pain relief score of 3.0 compared to 4.0 in the Vehicle group. There was a significant difference in the distribution of patients in the different pain relief categories in favor of the Ketorolac group ($p < 0.001$). There were fewer patients in the 'little' and 'no pain relief' categories in the Ketorolac group (46.2%, 36/78) compared to the Vehicle group (86.5%, 64/74). Results for pain relief at the 1st 12 hour period is presented in Table 15 below.

Table 15. Maximum Pain Relief in the First 12 Hour Period

Severity Category and Descriptive Statistics	Keto (N=79)	Vehicle (N=78)	Treatment P-value[a]
Complete pain relief	12 (15.4%)	0 (0.0)	<0.001

Great deal pain relief	16 (20 5%)	1 (1.4%)
Fair amount pain relief	14 (17.9%)	9 (12 2%)
Little pain relief	24 (30 8%)	29 (39 2%)
No pain relief	12 (15.4%)	35 (47.3%)
N	78	74
Mean	3.1	4 3
SD	1 32	0 74
Median	3.0	4.0
Min	1	2
Max	5	5

[a] P-values are from CMH test for row mean score differences with modified ridits, stratified by investigator.

Pain relief was also greater in the Ketorolac group during all remaining 12-hour post-PRK surgery periods (i.e., up to 108 hours post-PRK surgery). The median pain relief scores during all remaining 12-hour post-PRK surgery periods except the 3 rd period, were lower in the Ketorolac group (3.0, 4.0, 3.0, 3.0, 3 0, 2.0, 2.0, and 2.0, respectively) compared to the Vehicle group (4.0, 4.0, 4.0, 4 0, 4.0, 4.0, 4.0, and 4 0, respectively). There was a significant difference in the distribution of patients in the different pain relief categories during all remaining 12-hour post-PRK surgery periods in favor of the Ketorolac group ($p \leq 0.002$). There were fewer patients in the 'little' and 'no pain relief' categories in the Ketorolac group (32.9% [26/79]; 59.5% [47/79], 48.1% [38/79]; 38 0% [30/79]; 30.4% [24/79]; 27.8% [22/79]; 27.8% [22/79], and 27.8% [22/79], respectively) compared to the Vehicle group (71.40% [55/77]; 70.5% [55/78]; 71.8% [56/78]; 62.8% [49/78]; 57.7% [45/78]; 55.1% [43/78]; 55.1% [43/78]; and 55.1% [43/78], respectively).

Use of Escape Medication

During the 1st 12-hour post-PRK surgery period, significantly fewer patients in the Ketorolac group (46.8%, 37/79) took escape medication compared to the Vehicle group (92.3%, 72/78; $p < 0.001$). Use of escape medication was also significantly lower during the 2nd , 3rd , and 4th 12-hour post-PRK surgery periods in the Ketorolac group (38.0% [30/79], 41.8% [33/79], and 31.6% [25/79], respectively) compared to the Vehicle group (67.9% [53/78], 65.4% [51/78], and 52.6% [41/78], respectively; $p \leq 0.006$). There were no significant differences in the use of escape medication during the remaining 12-hour periods ($p \geq 0.093$). The number of patients using escape medication per 12-hour post-PRK surgery periods is summarized in Table 16 below.

Table 16. Number of Patients Using Escape Medication

12-Hour Periods Post-Surgery	Ketorolac N = 79 n (%)	Vehicle N = 78 n (%)	P-value[a]
N[b]	79	78	
1st 12-hour (0 to 12)	37 (46.8%)	72 (92 3%)	p < 0 001
2nd 12-hour (12 to 24)	30 (38.0%)	53 (67.9%)	p < 0.001
3rd 12-hour (24 to 36)	33 (41.8%)	51 (65.4%)	0.004
4th 12-hour (36 to 48)	25 (31.6%)	41 (52.6%)	0.006
5th 12-hour (48 to 60)	24 (30.4%)	15 (19.2%)	0.093
6th 12-hour (60 to 72)	9 (11.4%)	7 (9.0%)	0.595
7th 12-hour (72 to 84)	1 (1 3%)	0 (0.0%)	0 289
8th 12-hour (84 to 96)	1 (1.3%)	0 (0.0%)	0 289
9th 12-hour (96 to 108)	1 (1.3%)	0 (0.0%)	0 289

a P-values calculated from CMH test for general association using table scores, stratified by investigator
b If a patient did not record use of escape medication during a 12-hour post-PRK surgery period, then 'no use' was imputed for that period. Thus the N remained constant over the 12-hour post-PRK surgery periods

During the 1st 12-hour post-PRK surgery period, fewer tablets of escape medication were used in the Ketorolac group (median = 0.0 tablets) compared to the Vehicle group (median = 2.0 tablets). There was a significant difference in the distribution of the number of tablets of escape medication used by patients in favor of the Ketorolac group ($p < 0.001$). Fewer patients in the ketorolac group (29.1%, 23/79) reported using 2 tablets or more compared to the Vehicle group (76 9%, 60/78). The total number of tablets taken during each 12-hour period was summarized in Table 17 below.

Table 17. Total Number of Tablets Taken during the 1st 12-Hour Period

Number of Tablets and Descriptive Statistics	Keto (N=79)	Vehicle (N=78)	Treatment P-value[a]
None	42 (53.2%)	6 (7.7%)	<0.001
1 tablet	14 (17.7%)	12 (15.4%)	
2 tablets	20 (25.3%)	31 (39.7%)	
3 tablets	3 (3.8%)	22 (28.2%)	
4 or more tablet	0 (0.0)	7 (9.0%)	
N	79	78	
Mean	0.8	2 2	
SD	0.95	1.17	
Median	0 0	2 0	
Min	0	0	
Max	3	6	

[a] P- values are from CMH test for row mean score differences with modified ridits, stratified by investigator.

The median number of tablets used during the 2nd , 3rd , and 4th 12-hour post-PRK surgery periods (ie, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours) was lower in the Ketorolac group (0.0, 0.0, and 0.0 tablets, respectively) compared to the Vehicle group (1.0, 1.0, and 1.0 tablets, respectively). There was a significant difference in the distribution of the number of tablets of escape medication used by patients in favor of the Ketorolac group ($p \leq 0.010$). Fewer patients in the ketorolac group (11.4% [9/79]; 22.8% [18/79]; and 7.6% [6/79], respectively) reported using 2 tablets or more compared to the Vehicle group (25.6% [20/78]; 42.3% [33/78] and 9.0% [7/78], respectively).

Using the Wilcoxon rank sum test from a survival analysis, there was a significant difference in cumulative incidence rates of time to first use of escape medication in favor of the Ketorolac group ($p < 0.001$). The median time to 1st use of escape medication occurred by 18 hours in the Ketorolac group, compared to within the 1st 6 hours in the Vehicle group. The first use of escape medication occurred within the 1st 12-hour post-PRK surgery period for 46.8% of patients in the Ketorolac group compared to 92.3% of patients in the Vehicle group. The Kaplan-Meier estimator for cumulative incidence rates of time to first use of escape medication is presented in Figure a.2 in Appendix A.

Ocular Symptom

At day 1 (approximately 24 hours post-PRK surgery), the median severity scores for foreign body sensation, photophobia, burning/stinging, and tearing, were lower in the Ketorolac group (2.0, 2.0, 1.0 and 2.0, respectively) compared to those in the Vehicle group (3.0, 3.0, 3.0 and 3.0, respectively). For these ocular symptoms, at day 1, there was a significant difference in the distribution of patients in the different ocular symptom severity category in favor of the Ketorolac group ($p \leq 0.005$). There were fewer patients in the 'moderate' to 'severe' categories in the Ketorolac group compared to the Vehicle

group. There were no significant differences between treatment groups for these ocular symptoms at the other visits ($p \geq 0.073$). For the ocular symptom, itching, there were no significant differences between treatment groups at any of the visits during the treatment period ($p \geq 0.444$). There were no notable differences between treatment groups for any of the ocular symptoms during the post-treatment period.

2.3.2.2.4. Results across Centers and Subgroups

There were no significant treatment-by-center interactions in the analyses of pain intensity and escape medication. There was a significant treatment-by-center interaction in the analysis of pain relief during the 1st and the 4th 12-hour post-PRK surgery period ($p \leq 0.055$). For study site # 3755, a larger proportion of patients in the Ketorolac treatment group reported little or no pain relief in the 1st 12-hour period post-PRK (3/5 (60%) in Ketorolac group and 1/4 (25%) in Vehicle group). For all other investigators, a much larger proportion of patients in the Vehicle treatment group reported little or no pain relief in the 1st 12-hour post-PRK surgery period.

Per FDA's request, subgroup efficacy analysis was performed after excluding patients from study site # 3508 to determine the effect of this center's data on the results of the study. The results of the analyses of the primary, as well as secondary efficacy variables excluding data from study site # 3508 were similar to those obtained in the analyses including data from this site, indicating no significant impact of this site's data on the overall results of the study

2.3.3 Reviewer's Comments--Additional Information for Pain Intensity

The primary endpoint for both Studies 191578-002 and 191578-003 was maximum pain intensity during the first 12 hours post treatment. In both studies, pain intensity was recorded immediately before each dose of [redacted] and escape medication. Since escape medication was administrated as needed and the treatment medication was not administrated strictly according to the label instruction by patients (3 hours post-operatively, and then every 4 hours while awake), there is a big variation in the number of pain intensity records among patients: the range was 0 to 10 in Study 191578-002 and 1 to 9 in Study 191578-003. Since a patient with more pain measurement indicates more intolerable pain through the 12 hour time course than a patient with fewer pain measurements and with the same maximum pain, the following analyses were done to supplement the primary endpoint analyses (maximum pain intensity in the 1st 12 hour period): frequency of dosing and maximum pain in finer time intervals.

1. Frequency of Dosing. The frequency plots for the number of doses administrated by treatment are presented in Figures 3-6 below. In both studies, Ketorolac group administrated medicine less frequently than the Placebo group ($p<0.0001$). In both studies, the median number of dosing for the Ketorolac group and Vehicle groups were 3 and 5, respectively.

Figure 3. Distribution of Dosing Frequency in Ketorolac Group during the 1st 12 Hour Period (Study 191578-002)

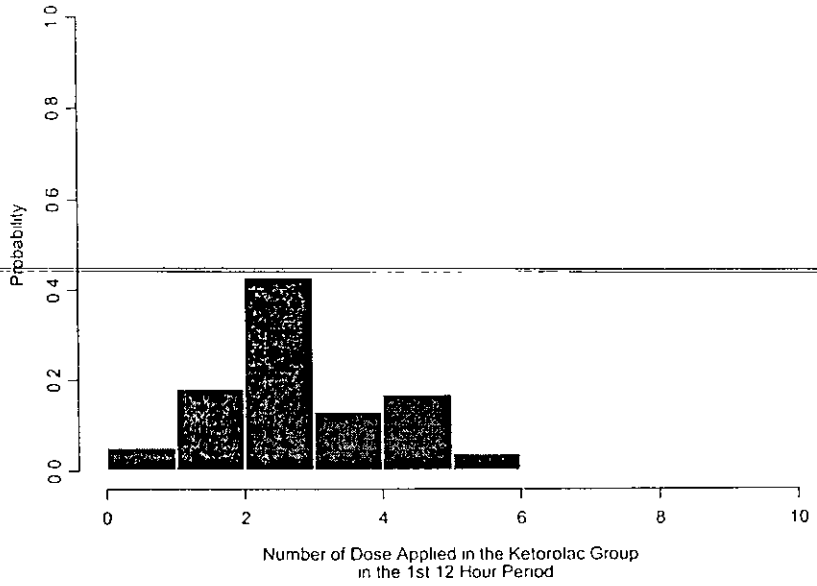


Figure 4. Distribution of Dosing Frequency in Placebo Group during the 1st 12 Hour Period (Study 191578-002)

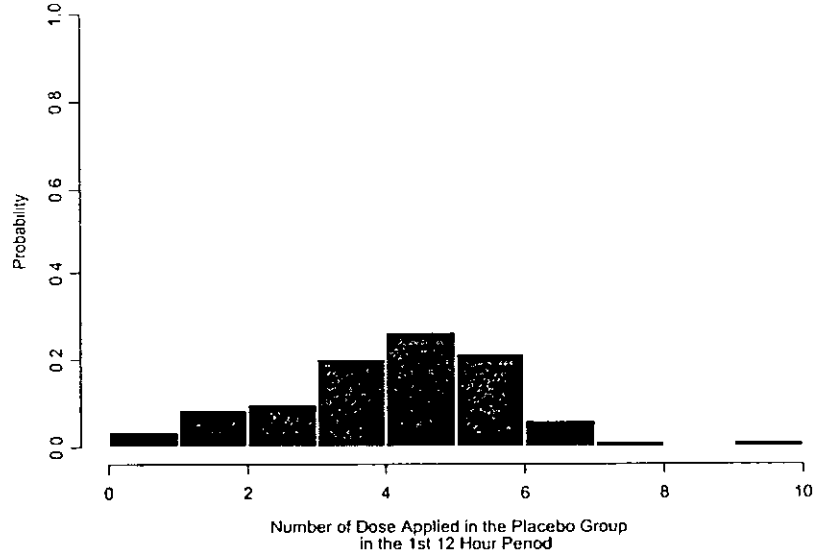


Figure 5. Distribution of Dosing Frequency in Ketorolac Group during the 1st 12 Hour Period (Study 191578-003)

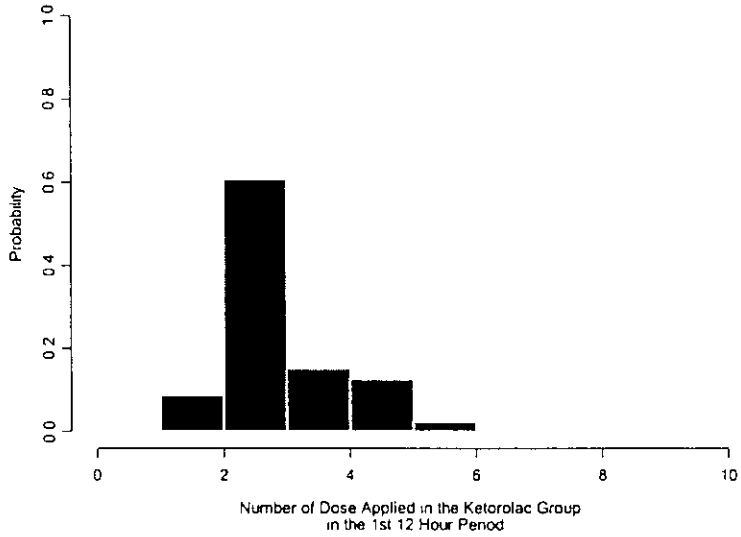
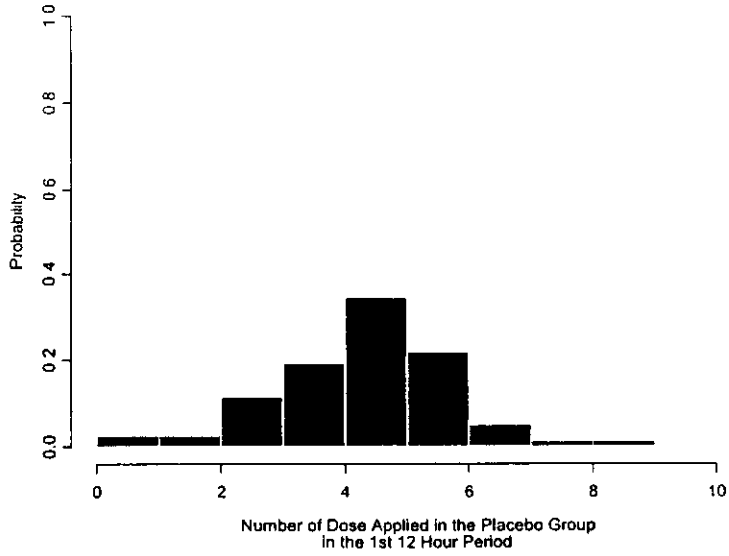


Figure 6. Distribution of Dosing Frequency in Placebo Group during the 1st 12 Hour Period (Study 191578-003)



2. This reviewer breaks the 12-hour period into smaller time intervals as 0-3 hours, 3-6 hours, 6-9 hours and 9-12 hours, and then check the consistency of the trend of the maximum pain intensities in these smaller time intervals vs. that of the 12-hour period. This analysis is exploratory without any imputation. Tables 18 and 19 below presents information for maximum pain intensity within each time interval. In both studies, the mean maximum pain intensities of the Ketorolac group were numerically lower than those of the Vehicle group except in the 0-3 hours interval. During the 0-3 hour period, there was a substantial amount of unavailable data in the Ketorolac group in both studies. This is due to the fact that most patients did not use any escape medication or study medicine in the Ketorolac group during this period, which in a way support the efficacy of Ketorolec.

Table 18. Maximum Pain Intensity within 3-Hour Intervals during the 1st 12 Hours (Study 191578-002)

Time Period	Treatment	N	Mean Pain Intensity	SD
0-3 Hours	Ketorolac	24 (31%)	2.38	0 97
	Placebo	53 (67%)	2 19	0.86
3-6 Hours	Ketorolac	65 (84%)	1.22	1 05
	Placebo	69 (87%)	2.61	0 93
6-9 Hours	Ketorolac	71 (92%)	1.20	1.04
	Placebo	74 (94%)	2.47	0 86
9-12 Hours	Ketorolac	60 (78%)	1.52	1 13
	Placebo	61 (77%)	2.38	0.99

Table 19. Maximum Pain Intensity within 3-Hour Intervals during the 1st 12 Hours (Study 191578-003)

Time Period	Treatment	N	Mean Pain Intensity	SD
0-3 Hours	Ketorolac	18 (23%)	2.67	1 14
	Placebo	50 (64%)	2.42	0.70
3-6 Hours	Ketorolac	73 (92%)	1.18	1.06
	Placebo	75 (96%)	2.61	0.77
6-9 Hours	Ketorolac	75 (95%)	1.33	1.21
	Placebo	72 (92%)	2.51	0 86
9-12 Hours	Ketorolac	66 (84%)	1.35	1.16
	Placebo	69 (88%)	2.35	0 98

The results in the above analysis generally support the finding in the primary endpoint. But due to the uncontrolled use of escape mediation, even with supportive result from use of escape medication (see table and figures), the effect of treatment medications can not be fully evaluated with separation from that of the escape medication.

2.4. Final Conclusion

Ketorolac has demonstarted superiority to Vehicle in terms of maximum pain intensity during the first 12 hour period post PRK surgery in both Studies 191578-002 and 191578-003. The superiority of Ketorolac is also supported by secondary findings in maximum pain intensity during the subsequent 12 hour periods post PRK surgery, first time to no pain, pain relief, use of escape medication, severity of ocular symptoms and

the results of subgroup analyses requested by FDA (excluding center 3753 in Study 191578-002 and excluding center 3508 in Study 191578-003).

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Appendix A. Figures

Figure a.1. The Kaplan-Meier Estimator for Cumulative Incidence Rates of First Use of Escape Medication (Study 151978-002)

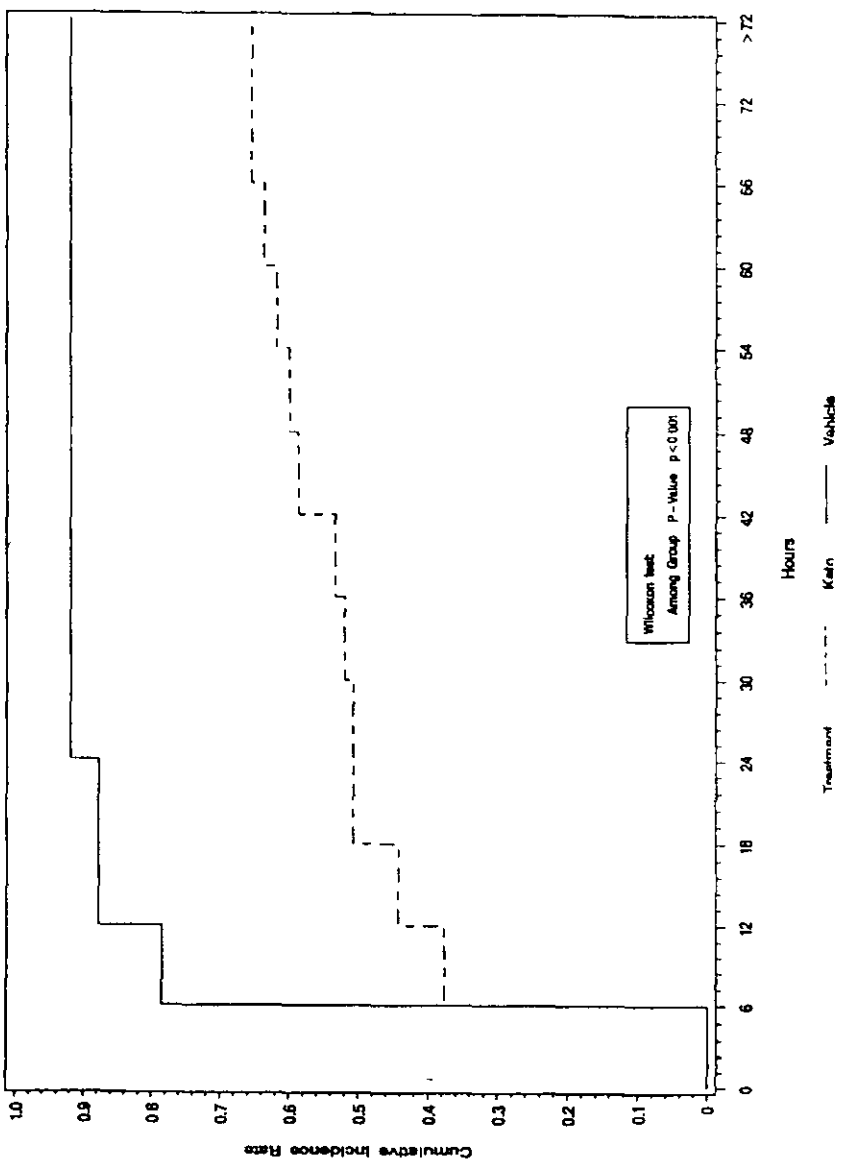
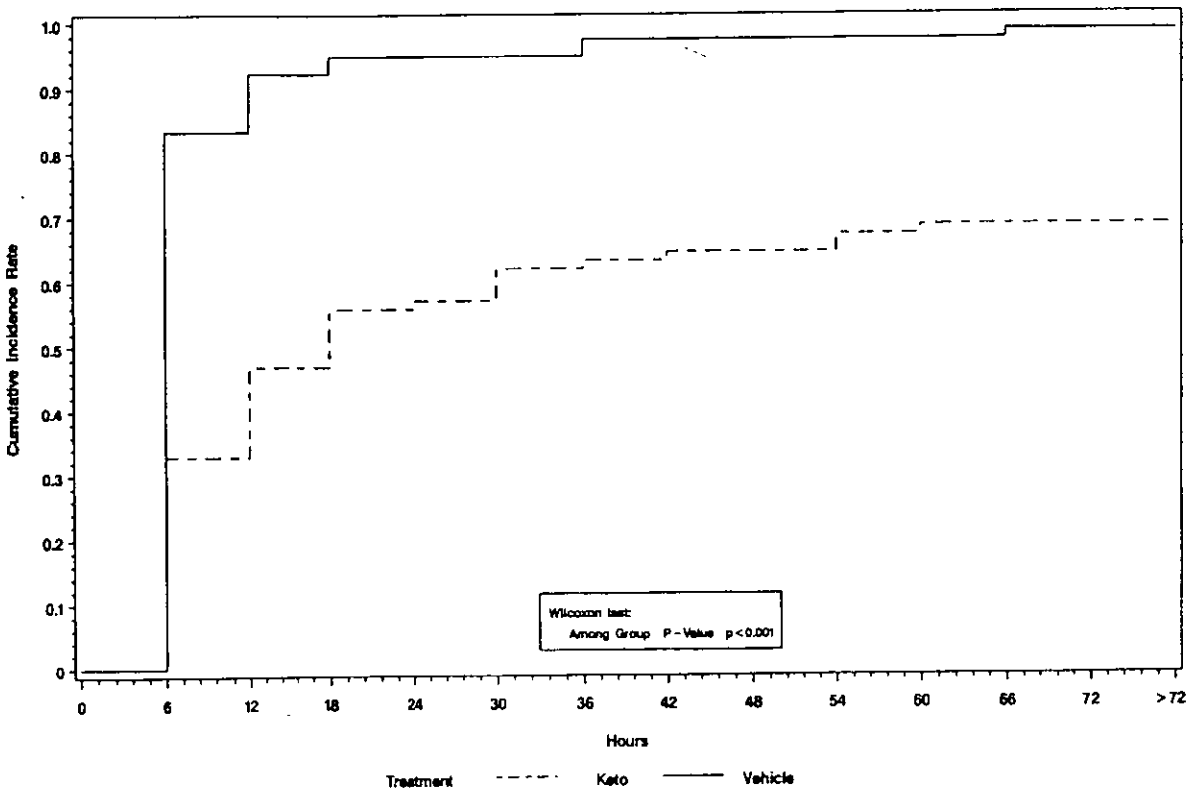


Figure a.2. The Kaplan-Meier Estimator for Cumulative Incidence Rates of First Use of Escape Medication (Study 191578-003)



Appendix B. Tables

Table b.1 Ocular Symptoms (Study 191578-002)

Ocular Symptoms	Severity Category and Descriptive Statistics	Keto (N=77)	Vehicle (N=79)	Treatment P-value[a]
Foreign Body Sensation	None	16 (20.8%)	11 (14 1%)	<0.001
	Trace	11 (14.3%)	6 (7 7%)	
	Mild	24 (31.2%)	13 (16.7%)	
	Moderate	21 (27.3%)	26 (33.3%)	
	Severe	5 (6.5%)	22 (28.2%)	
	N	77	78	
	Mean	1.8	2.5	
	SD	1.23	1.36	
	Median	2.0	3.0	
	Min	0	0	
	Max	4	4	
Photophobia	None	9 (11.7%)	6 (7.7%)	0.018
	Trace	6 (7.8%)	1 (1 3%)	
	Mild	22 (28.6%)	18 (23.1%)	
	Moderate	22 (28.6%)	26 (33.3%)	
	Severe	18 (23.4%)	27 (34.6%)	
	N	77	78	
	Mean	2.4	2.9	
	SD	1.26	1 15	
	Median	3.0	3.0	
	Min	0	0	
	Max	4	4	
Burning/Stinging	None	25 (32.5%)	17 (21.8%)	0.002
	Trace	14 (18.2%)	7 (9.0%)	
	Mild	22 (28.6%)	21 (26.9%)	
	Moderate	14 (18.2%)	15 (19.2%)	
	Severe	2 (2.6%)	18 (23.1%)	
	N	77	78	
	Mean	1 4	2 1	
	SD	1.19	1 44	
	Median	1.0	2 0	
	Min	0	0	
	Max	4	4	
Tearing	None	11 (14.3%)	2 (2.6%)	0.001
	Trace	7 (9.1%)	7 (9.0%)	
	Mild	19 (24.7%)	11 (14.1%)	
	Moderate	23 (29.9%)	27 (34.6%)	
	Severe	17 (22.1%)	31 (39.7%)	
	N	77	78	
	Mean	2.4	3 0	
	SD	1.32	1.07	
	Median	3.0	3.0	
	Min	0	0	
	Max	4	4	
Itching	None	57 (74.0%)	60 (76.9%)	0 756
	Trace	12 (15.6%)	7 (9.0%)	
	Mild	5 (6.5%)	4 (5.1%)	
	Moderate	3 (3.9%)	5 (6.4%)	
	Severe	0 (0.0)	2 (2.6%)	
	N	77	78	
	Mean	0.4	0.5	
	SD	0.78	1.03	
	Median	0.0	0.0	
	Min	0	0	
	Max	3	4	

[a] P- values are from Cochran- Mantel- Haenszel test for row mean score differences with modified ridits, stratified by investigator.

Table b.2 Ocular Symptoms (Study 191578-003)

Visit	Severity Category and Descriptive Statistics	Keto (N=79)	Vehicle (N=78)	Treatment P-value[a]
Foreign Body Sensation	None	17 (21 5%)	10 (12.8%)	0.005
	Trace	12 (15.2%)	5 (6.4%)	
	Mild	19 (24.1%)	20 (25.6%)	
	Moderate	26 (32.9%)	26 (33.3%)	
	Severe	5 (6.3%)	17 (21.8%)	
	N	79	78	
	Mean	1 9	2.4	
	SD	1 26	1.27	
	Median	2.0	3.0	
	Min	0	0	
	Max	4	4	
Photophobia	None	10 (12.7%)	2 (2.6%)	<0 001
	Trace	9 (11.4%)	3 (3.8%)	
	Mild	23 (29.1%)	11 (14.1%)	
	Moderate	24 (30.4%)	38 (48.7%)	
	Severe	13 (16.5%)	24 (30.8%)	
	N	79	78	
	Mean	2.3	3.0	
	SD	1.24	0.92	
	Median	2.0	3.0	
	Min	0	0	
	Max	4	4	
Burning/Stinging	None	26 (32.9%)	15 (19 2%)	<0 001
	Trace	16 (20.3%)	9 (11.5%)	
	Mild	14 (17.7%)	13 (16.7%)	
	Moderate	21 (26.6%)	23 (29.5%)	
	Severe	2 (2.5%)	18 (23 1%)	
	N	79	78	
	Mean	1.5	2 3	
	SD	1.27	1.44	
	Median	1.0	3.0	
	Min	0	0	
	Max	4	4	
Tearing	None	24 (30.4%)	11 (14.1%)	0.004
	Trace	6 (7.6%)	4 (5.1%)	
	Mild	12 (15.2%)	10 (12.8%)	
	Moderate	22 (27.8%)	31 (39.7%)	
	Severe	15 (19.0%)	22 (28.2%)	
	N	79	78	
	Mean	2.0	2.6	
	SD	1.54	1.33	
	Median	2.0	3.0	
	Min	0	0	
	Max	4	4	
Itching	None	60 (75.9%)	58 (74.4%)	0.715
	Trace	6 (7.6%)	5 (6.4%)	
	Mild	5 (6.3%)	7 (9.0%)	
	Moderate	7 (8.9%)	6 (7.7%)	
	Severe	1 (1.3%)	2 (2.6%)	
	N	79	78	
	Mean	0.5	0.6	
	SD	1.04	1.10	
	Median	0.0	0.0	
	Min	0	0	
	Max	4	4	

[a] P- values are from Cochran- Mantel- Haenszel test for row mean score differences with modified ridits, stratified by investigator.

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/s/

Hong Lu
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