CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-862

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: NDA 21-862

Drug Name: Nepafenac Ophthalmic Suspension 0.1%, three times daily

Proposed Indication(s): — treatment of inflammation and ocular pain associated with cataract surgery

Applicant: Alcon, Inc.

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Keywords:

NDA review, clinical studies, generalized estimating equations, mixed models

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Nepafenac Ophthalmic Suspension is a nonsteroidal anti-inflammatory drug (NSAID). The sponsor claimed that Nepafenac Ophthalmic Suspension, 0.1%, that was dosed three-time daily (TID) beginning one day prior to cataract surgery and continued on the day of surgery and for the first two weeks of the postoperative period — treated inflammation and ocular pain associated with cataract surgery. In this submission, there were two studies relevant to the indications: Studies C-02-53 and C-03-32. Furthermore, Study C-02-53 included four treatment groups: Nepafenac Ophthalmic Suspension, 0.1%, one-time daily (QD), twice-time daily (BID), TID and the vehicle. The Nepafenac QD and BID groups will not be reviewed in the report since they were not to evaluate the dose regimen that the sponsor is seeking for approval in this submission. The protocol-defined primary efficacy endpoint in Study C-02-53 was the percentage of patients declared as treatment failure, defined as a patient presenting at any postoperative visit with anterior chamber cell score >= 3, or anterior chamber flare score = 3, or ocular pain score > =4, while the protocol-defined primary efficacy endpoint in Study C-03-32 was the percentage of patients declared cure at Day 14, defined as aqueous cell score + aqueous flare score = 0 at Day 14. However, upon consultation with Drs. Wiley Chambers and Martin Nevitt, the two criteria used to evaluate the efficacy of Nepafenac Suspension for inflammation and pain associated with a cataract surgery in this study are as follows:

1. For post-cataract inflammation, at least one unit difference in the mean cell score during the post-operative period between the active and placebo groups is required. (According to Drs. Chambers and Nevitt, it means that the difference in the mean cell score during the post-operative period between the active and placebo groups is required to be statistically significant and the magnitude of treatment difference is at least one unit.)

2. For post-cataract pain, the difference in the percentage of pain-free patients during the post-operative period between the active and placebo groups is required to be statistically significant.

Additionally, according to Drs. Chambers and Nevitt, the following are the two alternative criteria for determining the efficacy of a drug for post-cataract inflammation and ocular pain.

1. For post-cataract inflammation, the difference in the percentage of the cured patients during the post-operative period between the active and placebo groups is required to be statistically significant.

2. For post-cataract ocular pain, the difference in the mean ocular pain score during the post-operative period between the active and placebo groups is required to be statistically significant; and the magnitude of the difference tends to be at 25%.

After reviewing the relevant endpoints and studies, I attained the following findings.

Study C-02-53

1. Nepafenac Suspension, 0.1%, TID group had statistically significantly different means for the cell score from the vehicle group at Days 3, 7 and 14. The difference in mean for the cell score between the Nepafenac Suspension and vehicle groups was -0.2, -0.5, -0.9 and -1.1 at Days 1, 3, 7 and 14, respectively. Thus, when compared to the vehicle, the Nepafenac Suspension, 0.1% TID reduced the mean for the cell score by at least one unit only at Day 14.

2. The proportions of ocular pain-free patients were statistically significantly different between the two study groups at all post-operative visits, with more patients free of ocular pain in the Nepafenac Suspension, 0.1%, TID group.

3. The differences in the cure rates on Days 3, 7 and 14 were statistically significantly different between the two treatment groups, with more cured patients in the Nepafenac Suspension, 0.1%, TID group.

4. The differences in the means for the ocular pain score between the two groups reached statistical significance at all post-operative visits. Furthermore, the Nepafenac Suspension, 0.1%, TID group appeared to reduce the means for the ocular pain by at least 25% compared to the vehicle at all post-operative visits.

Study C-03-32

1. The Nepafenac Suspension, 0.1%, TID group had statistically significantly different means for the cell score compared to the vehicle at all post-operative visits. The difference in mean for the cell score between the Nepafenac Suspension, 0.1%, TID and vehicle groups was -0.3, -0.7, -1.1 and -1.4 on Days 1, 3, 7 and 14, respectively. Nepafenac Suspension, 0.1%, TID reduced the cell score by at least one unit on Days 7 and 14 only.

2. The statistically significantly differences in the percentages of ocular pain-free patients between the two study groups were detected at all post-operative visits, with more pain-free patients in Nepafenac Suspension, 0.1%, TID group at each visit.

3. Nepafenac Suspension, 0.1%, TID had statistically significantly different cure rates compared to vehicle at Days 7 and 14. The sponsor's analysis used non-linear mixed-effect model and the estimates of the model parameters were heavily based on the data from Days 7 and 14. As a result, the differences between Nepafenac and vehicle groups in cure rate on Day 1 was also significant even though there was only one cured patient in the Nepafenac group and no cured patient in the vehicle group on that day. The sensitivity analysis using Fisher's exact test showed that the differences in the cure rates between the two groups at Days 1 and 3 were not significant. Therefore, the results on Days 1 and 3 were inconclusive.

4. The differences in the means for the ocular pain score between the two groups achieved statistical significance at all post-operative visits. Furthermore, the Nepafenac Suspension, 0.1%, TID appeared to reduce the ocular pain by at least 25% compared to the vehicle at all post-operative visits.

1.2 Brief Overview of Clinical Studies

Nepafenac, also known as amfenac amide, is the amide analog of 2-amino-3-benzoylbenzeneacetic acid. Although nepafenac is a new molecular entity, amfenac sodium (AHR 5850) has been on Japan market since 1986 in an oral dosage form for the treatment of pain and inflammation associated with rheumatoid and osteoarthritis and low back pain, as well as for the treatment of pain and inflammation following surgery, injury and tooth extraction. In this NDA, the sponsor is seeking the approval of Nepafenac Ophthalmic Suspension, 0.1%, using TID dosing regimen beginning one day prior to cataract surgery and continuing on the day of surgery and for the first two weeks of the postoperative period, to — reat the inflammation and ocular pain associated with cataract surgery. The NDA contained four randomized, placebo-controlled and multi-center studies: C-95-93, C-97-30, C-02-53, and C-03-32. Both Studies C-95-93 and C-97-30 consisted of multiple treatment arms with different concentrations of Nepafenac Suspension using four-times-daily (QID) dosing regimen. Also, patients in these two studies started to receive study medication one day after surgery and continued for 15 days. The studies were not designed to evaluate the efficacy of Nepafenac Suspension at the same dose level and dose regimen as those that this NDA is seeking for approval. Hence, I will focus on reviewing Studies C-02-53 and C-03-32. (Note that there were three Nepafenac, 0.1% groups using different dose regimen in Study C-02-53, the Nepafenac, 0.1%, TID group will be the focus of the review for the same reason.)

Studies C-02-53 and C-03-32 were multi-center, masked randomized, placebo-controlled, and parallel-group trials. A total of 228 eligible patients from 10 centers in the US in Study C-02-53 were evenly randomized to one of the six treatment groups, receiving either Nepafenac Ophthalmic Suspension 0.1% or vehicle with one drop either one, two or three times a day. A total of 522 patients from 22 centers in the US in Study C-03-32 were randomized into Nepafenac Ophthalmic Suspension 0.1% TID or placebo. Patients in both studies began dosing in operative eye one day prior to surgery, receiving an additional drop 30 to 120 minutes prior to surgery, and continued the treatment after surgery and for the following 14 days or until the treatment failure. The protocol-defined primary efficacy endpoint in Study C-02-53 was the percentage of patients declared as treatment failure, defined as a patient presenting at any postoperative visit with anterior chamber cell score >= 3, or anterior chamber flare score = 3, or ocular pain score > =4, while the protocol-defined primary efficacy endpoint in Study C-03-32 was the percentage of patients declared cure at Day 14, defined as aqueous cell score + aqueous flare score = 0 at Day 14. The grading criterion for anterior chamber cell and flare, and ocular pain are displayed in Table 1 below.

Table 1: Grading Criterion for Anterior Chamber Cell and Flare, and Ocular Pain

Anterior Chamber Cell					
Grade	0	1	2	3	4
Number of Cells	None	1 – 5 cells	6 - 15 cells	16 - 30 cells	Greater than 30 cells

Anterior Chamber Flare				
Grade	0	1	2	3
Flare	No visible flare when compared with the normal eye	Mild – Flare visible against dark papillary background but not visible against iris background	Moderate – Flare is visible with the slit-lamp beam aimed onto the iris surface as well as the dark papillary background	Severe – Very dense flare

Ocular Pain						
Grade	0	1	2	3	4	5
Ocular Pain	None	Patient reports present of mild sensation or discomfort typical of postoperative ocular surgery	Mild -- mild, tolerable aching of the eye	Moderate – moderate and more prolonged aching sufficient to require the use of OTC analgesics (e.g. acetaminophen)	Moderately severe – more prolonged aching requiring the use of an OTC analgesic other than acetaminophen	Severe – patient reports intense ocular, periocular or radiating pain requiring prescription analgesics

However, upon consultation with Drs. Chambers and Nevitt, , the following two criteria are used to determine the efficacy of the active treatment for post-cataract inflammation and ocular pain:

1. For post-cataract inflammation, at least one unit difference in the mean cell score during the post-operative period between the active and placebo groups is required. (In other words, the difference in the mean cell score during the post-operative period between the active and placebo groups is required to be statistically significant and the magnitude of treatment difference is at least one unit according to Drs. Chambers and Nevitt.)

2. For post-cataract pain, the difference in the percentage of pain-free patients during the post-operative period between the active and the placebo groups is required to be statistically significant.

In addition, according to Drs. Chambers and Nevitt, the following two criteria can be used alternatively to determine the efficacy of a treatment for post-cataract inflammation and pain.

1. For post-cataract inflammation, the difference in the percentage of the cured patients during the post-operative period between the active and the placebo groups is required to be statistically significant.

2. For post-cataract pain, the difference in the mean ocular pain score during the post-operative period between the active and placebo groups is required to be statistically significant; and the magnitude of the difference tends to be at 25%.

Due to the importance of the four parameters, I will concentrate on reviewing them and conduct the sensitivity analysis or post-hoc analysis if necessary even though most of the four parameters were not pre-specified in the protocol as primary endpoints.

1.3 Statistical Issues and Findings

Study C-02-53

1. The sponsor's ITT analysis included patients who received test article and returned for at least one post-surgical follow-up visit. In fact, all randomized patients receiving at least one dose of study medication should be included in the ITT analysis. The exclusion of patients who did not have post-surgical follow-up visit may lead to bias conclusion.

2. For the cell score, the sponsor used LOCF data to fit the mixed-effect model using compound symmetry covariance in the ITT analysis. This may lead to incorrect estimates of the convariance of the parameters, and therefore biased conclusions. The reviewer conducted two sensitivity analyses: the landmark analysis (fitting a linear regression model at each visit individually) using ITT with LOCF, and the mixed-effect model with unstructured convariance using ITT without imputation of missing data. The sensitivity analysis results were consistent with the sponsor's, i.e., the Nepafenac TID group had significantly different means for the cell score from those of the vehicle group at Days 3, 7 and 14.

3. For the percent of cured patients at each visit, the sponsor fitted a logistics regression using data from all visits, and then tested the treatment difference at each visit by comparing the least square (LS) means. The results indicated the cure rates at Days 7 and 14 were statistically significantly different between the two groups and the Nepafenac group had higher proportions of cured patients on both days. However, the sponsor's SAS program for the logistic regression was incorrect. Also, the numbers of cured patients on Days 1 and 3 in each treatment group were small and some of them were even zero. Therefore, the results from logistics regression may not be reliable. The sensitivity analysis using the Fisher's exact test or chi-square test for each visit revealed that the cure rates at Days 3, 7 and 14 were statistically significantly different between the Nepafenac and vehicle groups. Finally, due to the concern that the sponsor-defined ITT population may result in biased conclusions, I performed an additional sensitivity analysis, using all randomized patients who received at least one dose of study medication and considering those who did not have a post-operative visit as "not cured" patients. The Fisher's exact test or chi-square test was utilized to detect the treatment difference at each visit. I got the same results as the first sensitivity analysis.

Study C-03-32

1. Similar to Study C-02-53, the sponsor's defined the ITT population as all randomized patients who received test article, completed IOL implant surgery, and returned for at least one post-surgical follow-up visit. All randomized patients taking at least one dose of study medication should be included in the ITT analysis. The exclusion of patients who did not complete IOL implant surgery or who did not have post-surgical follow-up visit may lead to bias conclusion.

2. For the cell score, the sponsor again used LOCF data to fit the mixed-effect model using compound symmetry covariance in the ITT analysis. This may result in inaccurate estimates of covariance of the parameters, and therefore biased interferences. I again carried out two sensitivity analyses: the landmark analysis using ITT with LOCF, and the mixed-effect model with unstructured convariance using ITT without imputation of missing data. The sensitivity analysis results were consistent with the sponsor's, i.e., Nepafenac TID group had statistically significantly different means for the cell score compared to the vehicle group at all post-operative visits.

3. For the cure rate, the sponsor generated a non-linear mixed-effect model using the data from all visits, and then tested the treatment difference at each visit based on LS means. Fitting a non-linear mixed-effect model is sensitive to the initial values for parameter estimates. It is unclear how the sponsor obtained the starting values. Also, the parameter estimates were heavily based on the data from Days 7 and 14 where there were more cured patients and the differences between the two treatment groups in cure rate were large. As a result, the differences at all post-operative visits were statistically significant even on Day 1 when there was only one cured patient was in the Nepafenac group and no cured patients in vehicle group. The sensitivity analysis using Fisher's exact test or chi-square test performed at each visit demonstrated that there were significant differences in the cure rate on Days 7 and 14 only. Finally, due to the concern about the incorrect definition of the ITT population by the sponsor, I performed an additional sensitivity analysis including all randomized patients who took at least one dose of study medication and treating those who did not have a post-surgical follow-up visit or who did not complete IOL implant surgery as not cured patients. The Fisher's exact test or chi-square test was employed to evaluate the treatment difference at each visit. The results were consistent with the first sensitivity analysis.

2. INTRODUCTION

2.1 Overview

Nepafenac, also known as amfenac amide, is the amide analog of 2-amino-3-benzoylbenzeneacetic acid. Although nepafenac is a new molecular entity, amfenac sodium (AHR 5850) has been on Japan market since 1986 in an oral dosage form for the treatment of pain and inflammation associated with rheumatoid and osteoarthritis and low back pain, as well as for the treatment of pain and inflammation following surgery, injury and tooth extraction. Nepafenac rapidly penetrates the cornea and is converted to the active moiety amfenac by intraocular tissue hydrolases. The prodrug has very weak cyclooxygenase inhibitory activity whereas amfenac exhibits potent cyclooxygenase activity. Therefore, Alcon is developing Nepafenac Ophthalmic Suspension for the — ıreatment of pain and inflammation associated with cataract surgery. The product was submitted under IND 49,924 in February 1996 by Alcon Laboratories, Inc.. The ownership was transferred from Alcon Laboratories, Inc. to Alcon Universal, Ltd. in May 2001, and from Alcon Universal, Ltd. to Alcon, Inc. in November 2002. Notification of these changes has been submitted to the IND.

An End-of-Phase II/pre-NDA meeting was held on August 11, 2003 to review the Agency's agreement on the chemistry, non-clinical safety and clinical plan issues. With regard to the clinical plan for Study C-03-32, the Agency agreed that, based on the results of Study C-02-53, TID use of the 0.1% formulation demonstrated efficacy earlier than QD or BID dosing regimen to — treat post-cataract inflammation based on the percentage of cured patients even though there did not appear to be any difference between the doses at the end of the two week trial. The Agency also stated that the acceptable efficacy endpoints for post-cataract inflammation are either statistically superior percentage of cured patients (i.e. cell + flare = 0) in the test group compared to the vehicle group, or statistically superior mean cell score and at least one unit greater in the vehicle group compared to the test group. Note that the indication of ocular pain was not discussed in the meeting.

The current submission included four randomized, placebo-controlled and multi-center studies: C-95-93, C-97-30, C-02-53 and C-03-32. This review will focus on Study C-03-32 and Nepafenac, 0.1%, TID treatment group in Study C-02-53 since Studies C-95-93 and C-97-30 and the other Nepafenac treatment groups in Study C-02-53 were not designed to evaluate the dose level and dose regimen in the proposed indication.

2.2 Data Sources

The NDA was submitted in paper format. In response to FDA request, the sponsor submitted the completed datasets for efficacy analyses along with the SAS programs in CDs, and I received them on May 2, 2005. Table 2 lists the studies that are reviewed in this report.

Table 2: Reviewed Studies

Study Number Number of Center(s)	Study Design	Treatment Arms and Number of Randomized Patients
C-02-53 10 centers in US	Phase 2/3, multi-center, masked, randomized, placebo-controlled, parallel-group	• Nepafenac 0.1%, QD: 50 • Nepafenac 0.1%, BID: 53 • Nepafenac 0.1%, TID: 58 • vehicle (the combined vehicle posology groups): 59
C-03-32 22 centers in US	Phase 3, multi-center, masked, randomized, placebo-controlled, parallel-group	• Nepafenac 0.1%, TID: 245 • vehicle: 245

3. STATISTICAL EVALUATION

Studies C-02-53 and C-03-32 were reviewed individually as follows. Of note, the ITT hereafter refers to the ITT population defined by the sponsor.

3.1 Evaluation of Efficacy

3.1.1 Study C-02-53

3.1.1.1 Study Design and Efficacy Assessments

This study was a multi-center, masked, randomized, placebo-controlled, parallel-group trial. The primary objective of the study was to evaluate the efficacy and safety of topical ocular Nepafenac Ophthalmic Suspension 0.1%, given at pre- and post-operation, in treatment of inflammation after cataract extraction followed by implantation of a posterior chamber intraocular lens.

At the preoperative screening visit (six weeks to one day prior to the cataract surgery), all eligible patients were randomly assigned to one of the six treatment groups within center, receiving either Nepafenac Ophthalmic Suspension, 0.1% or Nepafenac vehicle with each treatment group dosing one drop either one, two, or three times a day. Treatment was initiated prophylactically one day before surgery, continued on the day of surgery (one drop was administered 30 to 120 minutes prior to surgery), and for 14 days following surgery or until treatment failure occurred. There were 4 scheduled postoperative visits: Day 1 (24 ± 4 hours), Day 3 (± 1 day), Day 7 (± 2 days), and Day 14 (-1 to +5 days) / early exit.

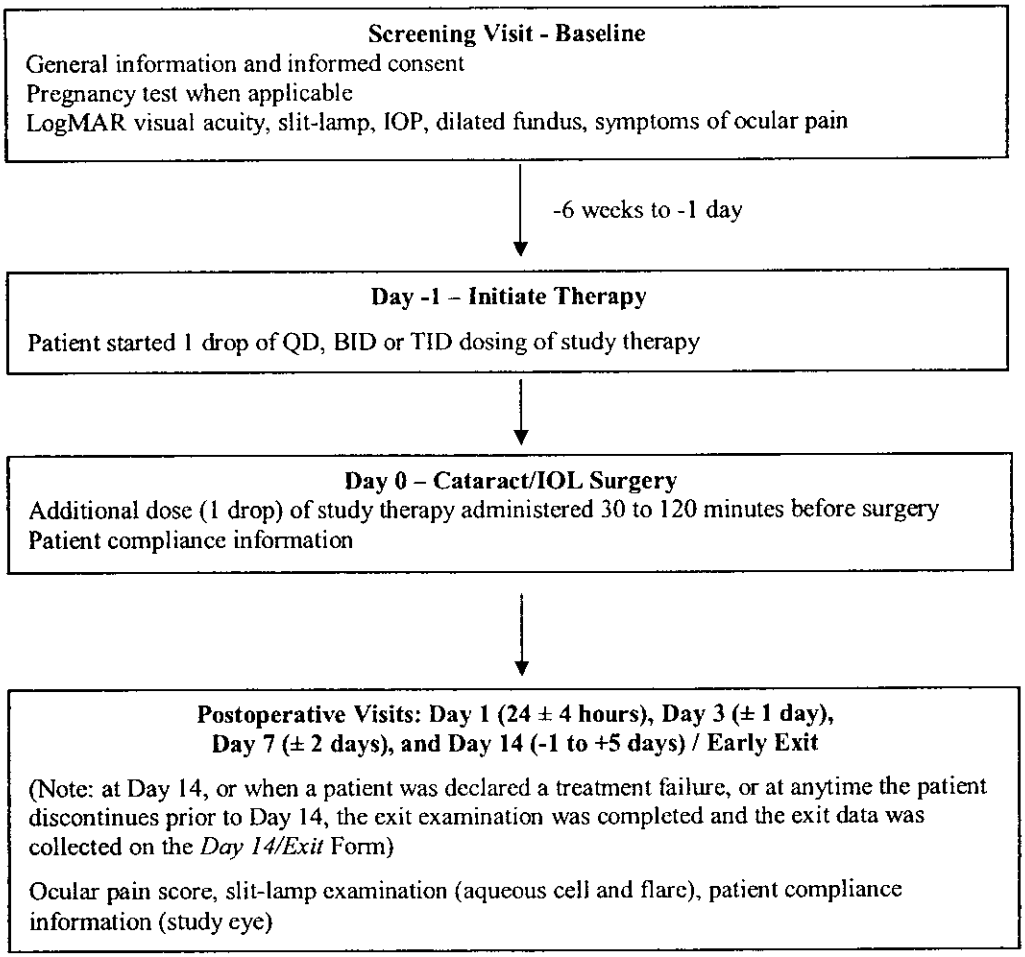
The efficacy measurements included anterior chamber cell and flare determined by the slit lamp examination, and ocular pain. These assessments were made at the screening visit and at the four postoperative visits. The measurements taken at the screening visit were treated as baseline. Figure 1 in next page displays the flow chart of study design and efficacy assessments.

The primary efficacy parameter was the percent of patients declared as treatment failure, defined as a patient presenting at any postoperative visit with a cell score of Grade 3 or greater, or flare score of Grade 3 or greater, or with moderately severe to severe ocular pain. The secondary efficacy variables were:

1. the percent of patients with clinically significant inflammation (defined as having a score of four or more for cell and flare combined) at each visit;
2. the percent of responders (defined as having less than five cells and no flare at that visit);
3. cell and flare scores.

The analyses for the percent of patients with clinically significant inflammation and the percent of responders consisted of the tests for individual treatment comparisons and the tests for increased response to dosing posology.

Figure 1: Study C-02-53, Flow Chart of Study Visits and Efficacy Measurements



Source: CSR-Clinical Study Report for Study C-02-53, Figures 9.1.-1 and 9.5.-1 in Section 9.1 in Vol. 8, Module 5, with some modifications by Karen Qi.

3.1.1.2 Patient Disposition, Demographics and Baseline Characteristics

The study was carried out in 10 centers in US. A total of 228 patients were randomized and dispensed masked study medication at the end of preoperative screening visit: 50 patients in Nepafenac 0.1% QD group, 53 in Nepafenac 0.1% BID group, 58 in Nepafenac 0.1% TID group, and 59 in the vehicle group (the combined vehicle posology groups). Eight patients, two in each treatment group, discontinued from the study prior to or at surgery and returned all study medications unopened. Eight of the remaining 220 patients were discontinued prior to or at surgery due to surgical problems unrelated to the study medication, and had no postoperative follow-up study examination. The ITT population included the remaining patients who received study medication and returned for at least one post-surgical follow-up visit. The PP population consisted of 198 patients who received a test article, completed intraocular lens (IOL) implant surgery, met the inclusion/exclusion criteria, and adhered to protocol guidelines. The 14 patients in the ITT analysis but excluded from the PP analyses had protocol deviation (contraindicated

medication used: seven patients; did not meet the inclusion/exclusion criteria: five patients; non-compliance with dosing of study medication: two patients). Table 3 presents patient's disposition.

Table 3: Study C-02-53, Patient Disposition (All Randomized)

	Total	Nepafenac 0.1% QD	Nepafenac 0.1% BID	Nepafenac 0.1% TID	vehicle
Total randomized	228	52	55	60	61
Not receiving any study medication	8	2	2	2	2
Receiving at least one study medication	220	50	53	58	59
Not having any post-surgical follow-up visit	8	2	3	2	1
Adverse event	1	1	0	0	0
Patient decision	2	0	1	1	0
Lost to follow-up	1	0	1	0	0
Other	4	1	1	1	1
Having at least one post-surgical follow-up visit	212	48	50	56	58
Completing study	132	31	34	44	23
Not completing study	80	17	16	12	35
Adverse event	5	4	1	0	0
Patient decision	2	0	1	1	0
Treatment failure	70	12	14	11	33
Other	3	1	0	0	2

Source: original NDA review by Karen Qi.

Of the 212 patients in the ITT analysis, the mean age was 70 years and ranged from 47 to 91 years. The majority of patients were female (57%) and Caucasian (79%). There were no differences across the treatment groups with respective to age, gender, race, iris color, and baseline aqueous cell, aqueous flare and ocular pain scores in the ITT population. Patient demographics and baseline characteristics in the ITT population are presented in Table 25 in Appendix 6.1.

3.1.1.3 Statistical Methodologies

1. Planned Analyses

The percent of patients declared as treatment failure in each of the Nepafenac groups was compared to that in placebo group, using Fisher's exact test (i.e., 3-test: TID, BID and QD versus placebo, respectively). Hommel's procedure was used to control the overall familywise error rate.

The comparisons of the percent of patients with clinically significant inflammation and the percentage of responders at each visit between the three Nepafenac groups (TID, BID and QD) versus placebo were made using repeated measures logistic regression (generalized estimating equations, Proc GENMOD from SAS), respectively. The fixed effects included treatment and visit, and the random effect was patient. An exchangeable covariance structure was used. The effect of multiple testing was examined using Hommel's procedure. A two-sided Jonkherri-Terpstra (J-T) test was used to test for changes in response due to increasing dosing frequency in percents of patients with clinically significant inflammation and responders, respectively.

Finally, the descriptive statistics were calculated for cell plus flare scores, cell scores, and flare scores. Repeated measure analysis of variance was used to compare means to placebo at each day. The fixed effects were treatment and visit, and the random effect was patient. A compound symmetry covariance structure was used. The effect of multiple testing was examined using Hommel's procedure.

Data from the operative eye were used for the analysis. The efficacy analysis was performed in both ITT and PP populations. The missing data in the analysis using the ITT population was imputed by LOCF, while the missing data in the PP population was not imputed. Inferences were primarily based upon the ITT population since this was a superiority study. Discrepancies (if any) between the PP and ITT results were examined to determine if non-evaluable cases influenced the results. Homogenous results for ITT and PP analyses implied that the results were robust with regards to missing non-evaluable observations.

2. Sample Size

A total of 192 patients were planned to enroll in the study, with 48 patients in each of the three Nepafenac groups and 16 patients in each of the three vehicle groups. According the sponsor, this sample size would provide 80% power in a comparison of proportions to detect a difference of percent of patients with treatment failures assuming that the percents in a treated group and the placebo group were 32.6% and 63%, respectively. Of note, as mentioned in the previous section, the actual study recruited 228 patients and 220 of them received at least one dose of study medication.

3. Changes in Planned Analyses Provided in Clinical Study Report

Additional post-hoc exploratory analyses of percent cures and ocular pain by treatment at each visit were performed. A patient was declared cured at a particular visit if they presented with

cell + flare = 0 at that and all subsequent visits. Logistic regression was used to test for treatment differences between the Nepafenac 0.1% treatment groups and placebo in the percent of patients declared cured overall and to each visit. Meanwhile, the distribution of pain (absent versus present) by visit for each Nepafenac treatment group was compared to the rates observed in the placebo group, using chi-square test.

3.1.1.4 Sponsor's Results

1. Primary Efficacy Analysis

The sponsor's ITT and PP analyses indicated that there was a significant difference in the rate of treatment failures at Day 14 between the Nepafenac TID and vehicle groups. Specifically, the rate of treatment failures at Day 14 was 19.6% and 60.3% for the vehicle and Nepafenac TID groups, respectively (Table 4). For completeness, the sponsor conducted the additional exploratory analysis for treatment failures by each visit. The ITT analysis showed a lower rate of treatment failures for each visit was observed in the Nepafenac TID group, and the treatment differences reached statistical significance at Days 3 and 7 (Table 5).

Table 4: Study C-02-53, Percent of Treatment Failures at Day 14 (ITT with LOCF)

	Total Patients	Treatment Failures		Raw P-Value	Hommel P-value
		N	%		
Nepafenac 0.1% TID	56	11	19.6	<0.0001	<0.0001
vehicle	58	35	60.3		

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.1-1 in Section 11.4.1.1 in Vol. 8, Module 5.
Overall P-value is from Fishers Exact test.
Raw P-values reflects treatment comparisons to vehicle.
Hommel P-value reflects treatment comparisons to vehicle controlling for the overall familywise error rate.

Table 5: Study C-02-53, Cumulative Percent of Treatment Failures by Treatment and Visit (ITT with LOCF)

		Total Patients	Treatment Failures		LSMeans P-Value
			N	%	
Day 1	**Nepafenac 0.1% TID**	56	8	14.3	0.5010
	vehicle	58	11	19.0	
Day 3	**Nepafenac 0.1% TID**	56	10	17.9	0.0080
	vehicle	58	23	39.7	
Day 7	**Nepafenac 0.1% TID**	56	11	19.6	<.0001
	vehicle	58	32	55.2	

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.1.1.1-1 in Section 11.4.1.1 in Vol. 8, Module 5.
LS Means P-value is from repeated measures logistic regression (Proc Genmod) comparisons of each treatment to vehicle.

2. Secondary Efficacy Analysis

Both ITT and PP analyses demonstrated that the differences between the two groups in the means for the cell score, flare score and cell plus flare score at Days 3, 7 and 14 were statistically significant, and the Nepafenac TID group appeared to have lower means for the cell score, flare score and cell plus flare score than those of placebo at these visits. Furthermore, the ITT analysis revealed statistically significant differences in the percentage of patients with clinically

significant inflammation for Days 3, 7 and 14 were detected. But the significant result at Day 7 could not be confirmed by the PP analysis. Finally, the ITT analysis resulted in significant treatment differences in the percentage of responders at Days 3, 7 and 14. However, the PP analysis did not support the significant result at Day 14. Table 6 below presents the results from the ITT analysis for the aqueous cell score, and the results for other secondary endpoints are provided in the tables in Appendix 6.1.

Table 6: Study C-02-53, Aqueous Cell Scores by Visit (ITT with LOCF)

		Mean	SD	N	Min	Max	LS Means P-Value
Day 1	Nepafenac 0.1% TID	1.6	0.9	56	0	4	0.2121
	vehicle	1.8	0.9	58	0	4	
Day 3	Nepafenac 0.1% TID	1.5	1.0	56	0	4	0.0071
	vehicle	2.0	1.0	58	0	4	
Day 7	Nepafenac 0.1% TID	1.2	1.2	56	0	4	<.0001
	vehicle	2.1	1.2	58	0	4	
Day 14	Nepafenac 0.1% TID	0.9	1.2	56	0	4	<.0001
	vehicle	2.0	1.4	58	0	4	

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.2.1-1 in Section 11.4.1.2 in Vol. 8, Module 5.
Test=ANOVA, ANOVA P-values are from LS Means treatment effect by day
LS Means P-value reflects comparison of test product to vehicle
Day1-Day14 effect is Repeated Measures ANOVA

3. Exploratory Analyses

The ITT analysis showed that a greater proportion of cured patients in Nepafenac TID group at each visit compared to the vehicle group, and the treatment differences achieved statistical significance on Days 7 and 14 (Table 7). However, the PP analysis found the treatment difference at Day 14 was not significant. Moreover, both ITT and PP analyses demonstrated that, when compared with the vehicle group, more patients in the Nepafenac TID group were ocular pain free at each visit, and the treatment differences were statistically significant for all visits. Table 8 presents the results for percent of pain-free patients from the ITT analysis.

Table 7: Study C-02-53, Percent of Patients Cured (cumulative) by Visit (ITT with LOCF)

		Total Patients	Cures		LS Means P-Value
			N	%	
Day 1	Nepafenac 0.1% TID	56	3	5.4	0.5850
	vehicle	58	0	0.0	
Day 3	Nepafenac 0.1% TID	56	8	14.3	0.0602
	vehicle	58	1	1.7	
Day 7	Nepafenac 0.1% TID	56	17	30.4	0.0144
	vehicle	58	6	10.3	
Day 14	Nepafenac 0.1% TID	56	26	46.4	0.0092
	vehicle	58	13	22.4	

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.3.1-1 in Section 11.4.1.3 in Vol. 8, Module 5.
Repeated Measures logistic regression main effect of treatment p-value = 0.0128.
Repeated Measures logistic regression treatment by visit interaction p-value = 0.6567.
LS Means P-value is from logistic regression (Proc Genmod) comparisons of each treatment to vehicle.

Table 8: Study C-02-53, Percent of Patients with No Ocular Pain by Visit (ITT with LOCF)

		Total Patients	Absence of Pain		Chi-Square P-Value
			N	%	
Day 1	Nepafenac 0.1% TID	56	45	80.4	0.0023
	vehicle	58	31	53.4	
Day 3	Nepafenac 0.1% TID	56	48	85.7	0.0002
	vehicle	58	31	53.4	
Day 7	Nepafenac 0.1% TID	56	52	92.9	<0.0001
	vehicle	58	31	53.4	
Day 14	Nepafenac 0.1% TID	56	55	98.2	<0.0001
	vehicle	58	36	62.1	

Source: CSR - Clinical Study Report for C-02-53, Table 11.4 1.3.2.1-1 in Section 11.4.1.3 in Vol. 8, Module 5.

3.1.1.4 Reviewer's Comments

1. ITT Population

In the protocol, the sponsor defined the ITT population as all patients receiving test article (Page 338 of CSR for Study C-02-53, Vol. 9, Module 5). In the final analysis, the sponsor changed the definition to all patients who received test article and returned for at least one post-surgical follow-up visit (Page 62 in Section 10 of CSR for Study C-02-53, Vol. 8, Module 5). The change was incorrect. The exclusion of patients who did not have post-surgical follow-up visit may lead to bias conclusion.

2. Repeated Measures Analysis

For all the secondary efficacy endpoints, the sponsor fitted the repeated measures ANOVAs using compound symmetry convariance structure or the repeated measures logistics regression models using exchangeable convariance structure. I have following three concerns.

1) In sponsor's ITT analysis, the missing data were imputed using LOCF before the repeated measure analysis was performed. In fact, only the observed data without imputation of missing data should be used in the repeated measure analysis. Otherwise, it may result in inaccurate conclusions, in the sense that LOCF artificially increases the correlation between observations within a subject and therefore leads to incorrect estimates of the standard error and correlation for the parameters.

2) The compound symmetry convariance structure in the repeated measures ANOVA and the exchangeable convariance structure in the repeated measures logistics regression models assume that the correlations between any two observations within an individual are constant. This may be inappropriate. In sponsor's ITT with LOCF analysis, all the imputed values for an individual are exactly the same as his last observed value, and so the correlations between the last observed value and an imputed value or between any imputed values are constant. However, the correlation between any two observed values may not be a constant. Generally, two measurements taken at adjacent times are very

likely to be more highly correlated than two measurements taken several time points apart.

3) The sponsor's SAS program for repeated measures logistic regression was incorrect as follows:

proc genmod data=sec_&dsn.1 descending;

...

*model &variable = treat visit_number treat*visit_number / d=bin* ***link=id*** *...;*

repeated subject=pat(inv) / type=exch;

...

The link function should be logit for logistic regression.

3. Cure Rate

The footnotes in Table 11.4.1.3.1-1 for cure rate in Section 11.4.1.3 in CSR (Page 105, Vol. 5, Module 5) are incorrect. Both CSR (Section 9.8 on Page 60, Vol. 9, Module 5) and the sponsor's SAS program indicated that logistic regression instead of repeated measures logistic regression was fitted using all the data, and then LS means were used for treatment comparison at each visit. Again, the sponsor's SAS program for logistics regression was incorrect. Additionally, since the numbers of cured patients at Days 1 and 3 in each treatment group were small and especially some of them even were zero, the results from logistic regression were questionable. (Note that the zero cell causes convergence problem when fitting the logistic regression model using PROC GENMOD in SAS.) I conducted a sensitivity analysis, using the Fisher's exact test or chi-square test to compare the cure rate between the Nepafenac TID and placebo groups at each visit (landmark analysis). The results were similar to the sponsor's, with one exception that a significant treatment difference at Day 3 was observed in the sensitivity analysis (Table 9).

Table 9: Study C-02-53, Reviewer's Landmark Analysis, Percent of Patients Cured by Visits (ITT with LOCF)

		Total Patients	Cures		P-value[a]
			N	%	
Day 1	**Nepafenac 0.1% TID**	56	3	5.4	0.1153
	vehicle	58	0	0.0	
Day 3	**Nepafenac 0.1% TID**	56	8	14.3	0.0155
	vehicle	58	1	1.7	
Day 7	**Nepafenac 0.1% TID**	56	17	30.4	0.0078
	vehicle	58	6	10.3	
Day 14	**Nepafenac 0.1% TID**	56	26	46.4	0.0069
	vehicle	58	13	22.4	

[a] The p-values for Days 1 and 3 were based on Fisher's exact tests; P-values for Days 7 and 14 were based on Chi-Square tests.

Finally, because of the concern that the analysis using sponsor-defined ITT population may lead to biased results, I also carried out a sensitivity analysis including all randomized patients who

received at least one dose of study medication and regarding those who did not have a post-operative follow-up visit as "not cured" patients. The Fisher's exact test or chi-square test was again employed to compare the cure rate between the two groups at each visit. The results were similar to those from first sensitivity analysis that are presented in Table 9, and therefore are not reported here.

4. Cell Score

Since using the LOCF data to fit the mixed-effect model with compound symmetry covariance structure in sponsor's ITT analysis may result in inaccurate findings, I carried out two sensitivity analyses:

a) one-way ANOVA including treatment as the factor (four groups) in the ITT population with LOCF, and testing the treatment difference by comparing the two corresponding LS means (landmark analysis),

b) mixed-effect model with unstructured convariance in the ITT population without imputation of missing data.

Table 10 presents the treatment difference between Nepafenac 0.1% TID versus the vehicle from the landmark analysis, while Table 12 provides the analysis results from the mixed-effect model. The Nepafenac, 0.1%, TID group appeared to have lower mean cell scores than the vehicle group at Days 3, 7 and 14 in all analyses. The difference in mean cell score between the Nepafenac 0.1% TID and vehicle groups was -0.2, -0.5, -0.9 and -1.1 on Days 1, 3, 7 and 14, respectively. Only the difference at Day 14 was numerically greater than one unit.

Table 10: Study C-02-53, Reviewer's Landmark Analysis, Cell Score (ITT with LOCF)

		LS mean difference from vehicle (Treatment – vehicle)		P-value*
		Estimate	Std Err	
Day 1	**Nepafenac 0.1% TID**	-0.3	0.2	0.1169
Day 3	**Nepafenac 0.1% TID**	-0.6	0.2	0.0034
Day 7	**Nepafenac 0.1% TID**	-0.9	0.2	<0.0001
Day 14	**Nepafenac 0.1% TID**	-1.1	0.2	<0.0001

*P-values are based on comparing LS means from one-way ANOVA with treatment as the factor.

Table 11: Study C-02-53, Reviewer, Number of Patients Having Cell Scores by Visit[1] (ITT)

	Nepafenac 0.1% QD (N=48)	Nepafenac 0.1% BID (N=50)	Nepafenac 0.1% TID (N=56)	vehicle (N=58)
Day 1	48 (100%)	50 (100%)	56 (100%)	58 (100%)
Day 3	38 (79.2%)	40 (80.0%)	47 (83.9%)	45 (77.6%)
Day 7	32 (66.7%)	37 (74.0%)	45 (80.4%)	33 (56.9%)
Day 14	31 (64.6%)	35 (70.0%)	44 (78.6%)	25 (43.1%)

[1]These are the numbers of observations used in the mixed-effect model, and the results from the mixed-effect model are given in Table 12.

Table 12: Study C-02-53, Reviewer's Mixed-Effect Model using Unstructured Convariance (ITT without Imputation of Missing Data)

		LS mean difference from vehicle (Treatment – vehicle)		P-value for test of |difference| = 0
		Estimate	Std Err	
Day 1	Nepafenac 0.1% QD	-0.1	0.2	0.6621
	Nepafenac 0.1% BID	-0.1	0.2	0.3874
	Nepafenac 0.1% TID	-0.3	0.2	0.1169
Day 3	Nepafenac 0.1% QD	-0.4	0.2	0.0266
	Nepafenac 0.1% BID	-0.5	0.2	0.0121
	Nepafenac 0.1% TID	-0.6	0.2	0.0012
Day 7	Nepafenac 0.1% QD	-0.7	0.2	0.0050
	Nepafenac 0.1% BID	-0.6	0.2	0.0093
	Nepafenac 0.1% TID	-0.9	0.2	<0.0001
Day 14	Nepafenac 0.1% QD	-0.7	0.2	0.0004
	Nepafenac 0.1% BID	-0.6	0.2	0.0037
	Nepafenac 0.1% TID	-0.7	0.2	0.0003

5. Percent of Patients with No Ocular Pain

Due to the same concern that the sponsor-defined ITT population may lead to biased conclusion, I carried out a sensitivity analysis including all randomized patients taking at least one dose of study medication and considering those who did not have a post-operative follow-up visit as patients with ocular pain. The Fisher's exact test or chi-square test was used to compare the proportion of patients without ocular pain between the two groups at each visit. The results were similar to the sponsor's that displayed in Table 8 above.

6. Ocular Pain Score

With respect to the ocular pain score, I assessed the treatment effect at each visit by comparing the corresponding two least square (LS) means from one-way ANOVA with treatment (four groups: Nepafenac QD, BID, TID, and vehicle) as the factor (landmark analysis). Table 13 gives the descriptive statistics for ocular pain score in the Nepafenac TID and vehicle groups, and Table 14 presents the analysis results from the landmark analysis for the two groups. There were statistically significant differences in mean ocular pain score between the two groups at all post-operative visits, and the differences appeared to be at least 25%.

Table 13: Study C-02-53, Reviewer, Distribution of Ocular Pain by Visit (ITT with LOCF)

		N	Mean	SD	Min	Max
Day 1						
	Nepafenac 0.1% TID	56	0.2	0.5	0	2
	Vehicle	58	0.7	0.9	0	3
Day 3						
	Nepafenac 0.1% TID	56	0.1	0.4	0	1
	Vehicle	58	0.7	1.0	0	4
Day 7						
	Nepafenac 0.1% TID	56	0.1	0.3	0	1
	Vehicle	58	0.9	1.3	0	5
Day 14						
	Nepafenac 0.1% TID	56	0.0	0.1	0	1
	Vehicle	68	0.9	1.4	0	5

Table 14: Study C-02-53, Reviewer's Landmark Analysis, Ocular Pain Score (ITT with LOCF)

		LS mean difference from vehicle (Treatment – vehicle)		P-value*
		Estimate	Std Err	
Day 1	Nepafenac 0.1% TID	-0.4	0.1	0.0007
Day 3	Nepafenac 0.1% TID	-0.6	0.1	<0.0001
Day 7	Nepafenac 0.1% TID	-0.9	0.1	<0.0001
Day 14	Nepafenac 0.1% TID	-0.9	0.1	<0.0001

*P-values are based on comparing LS means from one-way ANOVA with treatment as the factor.

Dr. Wiley Chambers expressed the importance of consistency of the results from ITT and PP analyses for the ocular pain. Therefore, I performed the analysis using the data from PP population as well. The results were consistent with those from the ITT population and therefore are not provided.

3.1.2 Study C-03-32

3.1.2.1 Study Design and Efficacy Assessments

This was a multi-center, masked, randomized, placebo-controlled, parallel-group clinical trial with two treatment groups: Nepafenac Ophthalmic Suspension 0.1%, QID and placebo (Nepafenac Ophthalmic vehicle). The objective of the study was to evaluate efficacy and safety of the topical ocular Nepafenac Ophthalmic Suspension 0.1%, QID, given at pre- and post-operation, in treatment of patients with inflammation after cataract surgery and IOL implantation.

The study had almost the same efficacy assessments and the schedules for the study visits as Study C-02-53 (see Figure 1), with the only difference in that the study required the screening examination was performed six weeks to **two** days prior to the surgery. All eligible subjects were randomized on 1:1 ratio into the 2 treatment group at the screening visit. Similar to Study C-02-53, subjects began dosing in operative eye one day prior to surgery, received an additional

drop 30 to 120 minutes prior to the surgery, and continued the treatment (three times per day in this study) after surgery and for the following 14 days or until the treatment failure occurred.

The primary efficacy parameter was the percent of subjects declared cure at Day 14, defined as aqueous cell score + aqueous flare score = 0 at Day 14. The secondary efficacy variables included:

1. the percent of subjects declared treatment failures (defined as aqueous cell score >= 3, or flare score = 3, or ocular pain score >= 4 at any time postoperatively) at each visit;
2. the percent of subjects declared pain-free based on ocular pain scores;
3. the percent of subjects with clinically significant inflammation (defined as having a score of 4 or more for cell and flare combined).

Exploratory analyses were conducted on the percent of cures by visit, aqueous cell scores, flare scores, and aqueous cell plus flare scores.

3.1.2.2 Patient Disposition, Demographics and Baseline Characteristics

The study was conducted in 21 US centers. A total of 522 patients were randomized into study: 262 patient in Nepafenac group, and 260 in vehicle group. Thirty-five patients (15 in Nepafenac group and 20 in vehicle group) discontinued from the study prior to surgery and did not take any study medication. Of the 487 patients who potentially received study medication, 11 patients did not have any on-therapy postoperative study visits, including three patients who withdrew their consent prior to surgery, four patients who were discontinued prior to surgery (three due to use of contraindicated medication, and one due to non-compliance, three patients who were discontinued at surgery due to a surgical complication with the need for subsequent initiation of steroid therapy, and one patient who was lost-to-follow-up. The ITT analysis included the rest of 476 patients who received a test article, completed IOL implant surgery, and attended at least one post-surgical follow-up. The PP analysis excluded 33 patients in the ITT population due to a significant protocol violation (n=27), or due to a complicated/difficult surgery (n=6). Table 15 below presents the detailed information on patient's disposition.

Table 15: Study C-03-32, Patient Disposition (All Randomized)

	Total	Nepafenac 0.1% TID	vehicle
Total randomized	522	262	260
Not receiving any study medication	35 (6.7%)	15 (5.7%)	20 (7.7%)
Patient decision	16 (3.1%)	8 (3.1%)	8 (3.1%)
Noncompliance	1 (0.2%)	0 (0%)	1 (<0.1%)
Other	18 (3.4%)	7 (2.7%)	11 (4.2%)
Receiving at least one study medication	487 (93.3%)	247 (94.3%)	240 (92.3%)
Not having any post-surgical follow-up visit	11 (2.1%)	4 (1.5%)	7 (2.7%)
Patient decision	3 (0.1%)	2 (0.1%)	1 (<0.1%)
Noncompliance	1 (<0.1%)	0 (0%)	1 (<0.1%)
Other	7 (1.3%)	2 (0.1%)	5 (1.9%)
Having at least one post-surgical follow-up visit	476 (91.2%)	243 (92.7%)	233 (89.6%)
Completing study	303 (58.0%)	222 (84.7%)	81 (31.2%)
Not completing study	173 (33.1%)	21 (8.0%)	152 (58.5%)
Adverse event	7 (1.3%)	1 (<0.1%)	6 (2.3%)
Patient decision	4 (0.1%)	0 (0%)	4 (1.5%)
Treatment failure	159 (30.5%)	20 (7.6%)	139 (53.5%)
Other	3 (0.1%)	0 (0%)	3 (1.2%)

Of the 476 patients in the ITT population, the mean age was 70 years and ranged from 27 to 90 years. The majority of patients were female (56%) and Caucasian (90%). There were no differences across the treatment groups with respect to age, gender, race, iris color, baseline cell, flare and ocular pain scores in ITT population. The analysis in the PP population provided similar results. The patient demographics and baseline characteristics in ITT population are presented in Table 30 in Appendix 6.2.

3.1.2.3 Statistical Methodologies

1. Planned Analyses

Fisher's exact test was used to compare the primary parameter, the percent of subjects declared cure at Day 14, between Nepafenac and placebo groups.

In the secondary efficacy analyses, logistic regression (nonlinear mixed model with maximum likelihood estimation from Proc NLMixed of SAS) was employed for treatment comparisons for the incidence of treatment failures, the incidence of clinically significant inflammation and the incidence of patients reporting no pain. The fixed effects were treatment and visit, and the random effect was center. A binomial distribution was specified for the dependent variable; while a normal distribution was specified for random effects.

In the exploratory analyses, the statistical model to analyze the percent of cures by visit was identical to those for the secondary analysis. The analysis of cell score, flare score and cell plus flare score were conducted with a repeated measures analysis of variance. The fixed effects were

treatment and visit, and the random effect was subject. A compound symmetry covariance structure was used (PROC Mixed of SAS).

Data from the operative eye were used for the analysis. Efficacy analyses were conducted using both ITT and PP populations. The ITT analysis consisted of all subjects receiving a test article, complete IOL implant surgery, and attending at least one post-surgical follow-up. The PP analysis included subjects who received a test article, completed IOL implant surgery, met the inclusion/exclusion criteria and adhered to protocol guidelines. The values for dropouts and missing data in the time dependent analyses in the ITT population were imputed using LOCF, while no imputation was carried out in the PP population. Inferences were primarily based upon the ITT population since this was a superiority study. Discrepancies (if any) between the PP and ITT results were examined to determine in non-evaluable cases influenced the results. Homogenous results for the ITT and PP analyses implied that the results were robust with regards to missing non-evaluable observations.

2. Sample Size

A total of 432 patients were planned to enroll, with 218 patients in each treatment group. According to the sponsor, this sample size gave 80% power to detect treatment difference if the observed proportion of cures in Nepafenac treatment group was as low as 0.3700 compared to a placebo group rate of 0.2414; or if the observed placebo group rate was as high as 0.2599 compared to a Nepafenac treatment group rate of 0.3899. (Note that the 0.3899 cure rate in the Nepafenac group was based on a one-sided lower 80% confidence interval on the cure rate observed in Study C-02-53.) A total of 522 patients were randomized in the actual study, and 487 of them received at least one dose of study medication.

3. Additional Analysis Provided in Clinical Study Report

Additional post-hoc exploratory analysis on ocular pain by treatment across all visits was performed. Fisher's exact test was used to test for differences in the distribution of reported pain frequency for Nepafenac group relative to the placebo control.

3.1.2.4 Sponsor's Results

1. Primary Analysis

The sponsor's primary analysis results demonstrated that the difference between the Nepafenac and vehicle groups in cure rate at Day 14 was statistically significant, and the Nepafenac group appeared to have a higher cure rate (Table 16).

Table 16: Study C-03-32, Percent Cures at Day 14 (ITT with LOCF)

Treatment	Total	Day 14 Cures	
	N[a]	N	%
Nepafenac 0.1%, TID	243	152	62.6
vehicle	233	40	17.2

Source: CSR – Clinical Study Report for C-03-32, Table 11.4 1.1-1 in Section 11.4.1.1 in Vol. 12, Module 5.
Fishers Exact P-value <0.0001
[a] Patients who discontinued due to treatment failure were included in the Total N.

For completeness, the sponsor performed additional analyses for the cure rate, cell score, flare score, and cell plus flare score by each visit. Both ITT and PP analysis indicated there exited significant treatment differences favoring the Nepafenac treatment in all of these parameters at all postoperative visits. Tables 17 and 18 display the sponsor's analysis results for the cure rate and aqueous cell score, respectively. The analysis results for the flare score and the cell plus flare score are presented in the tables in Appendix 6.2.

Table 17: Study C-03-32, Cumulative Percent Cures by Visit (ITT with LOCF)

Treatment	Total N[a]	Day 1		Day 3		Day 7		Day 14	
		N	%	N	%	N	%	N	%
Nepafenac 0.1%	243	1	0	16	7	72	30	152	63
Vehicle	233	0	0	7	3	7	3	40	17
P-value		0.0050		0.0012		<0.0001		<0.0001	

Source: CSR – Clinical Study Report for Study C-03-32, Table 11.4.1.1.1-1 in Section 11.4.1.1 in Vol. 12, Module 5.
NL Mixed Model P-value = 0.0038; main effect of treatment
Cure defined as aqueous cell score plus aqueous flare score = 0 at current and at all subsequent study visits through to Day 14 final visit.
[a]Patients who discontinued due to treatment failure were included in the Total N.

Table 18: Study C-03-32, Aqueous Cell Score by Treatment and Visit (ITT with LOCF)

		Baseline	Day 1	Day 3	Day 7	Day 14
Nepafenac 0.1%	**N**	243	243	243	243	243
	Mean (SD)	0.0 (0.0)	1.6 (0.6)	1.3 (0.8)	1.0 (0.9)	0.6 (1.0)
	Min-Max	0-0	0-4	0-4	0-4	0-4
Vehicle	**N**	233	233	233	233	233
	Mean (SD)	0.0 (0.0)	1.9 (0.8)	2.0 (1.0)	2.1 (1.0)	2.0 (1.2)
	Min-Max	0-0	1-4	0-4	0-4	0-4
P-value		NA	0.0001	<0.0001	<0.0001	<0.0001

Source: CSR – Clinical Study Report for Study C-03-32, Table 11.4.1.1.1-2 in Section 11.4.1.1 in Vol. 12, Module 5.
Baseline P-value is from T-Test
Non-baseline P-values are LS Means by Visit
Repeated Measures ANOVA Main Effect of Treatment P-value <0.0001

2. Secondary Analyses

The results from the secondary efficacy analyses provided further support of effectiveness of the Nepafenac treatment. Specifically, the Nepafenac treatment was superior to vehicle in all secondary efficacy analyses, in the sense that, at all post-operative visits, Nepafenac treatment resulted in fewer patients with clinically significant ocular inflammation, fewer treatment failures and a greater percentage of pain-free patients in both ITT and PP analyses. Table 19 presents the results for percent of pain-free patients. The results of other secondary analyses are given in the tables in Append 6.2.

Table 19: Study C-03-32, Percent of Pain-free Patients by Visit (ITT with LOCF)

Treatment	Total N	Day 1		Day 3		Day 7		Day 14	
		N	%	N	%	N	%	N	%
Nepafenac 0.1%	243	202	83.1	221	90.9	217	89.3	226	93.0
Vehicle	233	97	41.6	108	46.4	103	44.2	105	45.1
P-value		<0.0001		<0.0001		<0.0001		<0.0001	

Source: CSR – Clinical Study Report for Study C-03-32, Table 11.4.1.2.3-1 in Section 11.4.1.2 in Vol. 12, Module 5.
NL Mixed model P-value <0.0001; main effect of treatment
Pain-free defined as ocular pain score = 0

3.1.4.5 Reviewer's Comments

1. ITT Population

The sponsor's ITT population included all randomized patients who received a test article, completed IOL implant surgery, and had at least one post-surgical follow-up. Again, this is inappropriate. The ITT analysis should include all randomized patients who received at least one dose of study medication.

2. Mixed-Effect Models

In the secondary and exploratory analyses, the sponsor used linear mixed-effect models for continuous endpoints and non-linear mixed-effect models for binary endpoints. I have the following three concerns.

1) Similar to Study C-02-53, the sponsor imputed the missing data using LOCF before fitting the mixed-effect models in ITT analysis, and used compound symmetric convariance structure in the linear mixed-effect models. These again are improper and may lead to biased conclusions.
2) It is unclear why the sponsor considered subject as random effect in the linear mixed-effect models, but center as random effect in the non-linear mixed-effect models.
3) Fitting non-linear mixed-effect model is sensitive to the starting values for parameter estimates. It is unclear how the sponsor obtained the initial values.

3. Cure Rate

The sponsor's result from the non-linear mixed-effect model indicated the cure rate in Day 1 was significantly different between the two treatment groups even though there was only one cured patient in the Nepafenac group and no cured patient in the vehicle group on that day. This

problematic result is likely due to the fact that the estimates of the model parameters were heavily driven by the data at Days 7 and 14 where more cured patients were observed and the differences in cure rate between the two treatment groups were large. I did a sensitivity analysis using Fisher's exact test or chi-square test to compare cure rate between the two treatment groups at each post-operative visit. The sensitivity analysis results revealed that the significant different cure rates were detected on Days 7 and 14 only (Table 20).

Table 20: Study C-03-32, Reviewer's Landmark Analysis, Percent Cures by Visit (ITT with LOCF)

Treatment	Total N[a]	Day 1		Day 3		Day 7		Day 14	
		N	%	N	%	N	%	N	%
Nepafenac 0.1%	243	1	0	16	7	72	30	152	63
vehicle	233	0	0	7	3	7	3	40	17
P-Value[b]		1.000		0.0869		<0.0001		<0.0001	

[a] Patients who discontinued due to treatment failure were included in the Total N.

[b] P-values for Days 1 and 3 were based on Fisher's exact test; and p-values for Days 7 and 14 were based on Chi-square test.

Again, due to the concern that the sponsor's ITT analysis excluding those patients who did not have a post-operative follow-up visit or did not complete IOL implant surgery may lead to bias results, I performed landmark analysis including all randomized patients who took at least one dose of study medication and treating those who did not have a post-operative follow-up visit or did not complete IOL implant surgery as "not cured" patients. The results were similar to those presented in Table 20, and therefore are not reported.

4. Cell Score

Because using LOCF data to fit the mixed-effect model with compound symmetry covariance structure in ITT analysis may result in biased inferences, I again performed two sensitivity analyses: the landmark analysis using ITT population with LOCF, and the mixed-effect model with unstructured covariance using incomplete ITT data. The results of sensitivity analysis were consistent with the sponsor's analysis, that is, the means cell scores in Nepafenac group were significantly lower than those of placebo at all post-operative visits (Tables 21-23). In addition, as shown in Table 24, the difference in mean cell score between Nepafenac and vehicle groups was -0.3, -0.7, -1.1 and -1.4 on Days 1, 3, 7 and 14, respectively. Hence, Nepafenac Suspension, 0.1%, TID reduced the cell score by at least one unit on Days 7 and 14 only.

Table 21: Study C-03-32, Reviewer's Landmark Analysis, Cell Score by Visit (ITT with LOCF)

	LS mean difference between Nepafenac and vehicle (Nepafenac – vehicle)		P-value for test of |difference| = 0
	Estimate	Std Err	
Day 1	-0.3	0.1	<0.0001
Day 3	-0.7	0.1	<0.0001
Day 7	-1.2	0.1	<0.0001
Day 14	-1.4	0.1	<0.0001

Table 22: Study C-03-32, Reviewer: Number of Patients Having Cell Scores by Visit[1]

	Nepafenac 0.1% TID (N=243)	vehicle (N=233)
Day 1	243 (100%)	233 (100%)
Day 3	229 (94%)	176 (76%)
Day 7	228 (94%)	121 (52%)
Day 14	223 (92%)	81 (35%)

[1]These are the numbers of observations used in the mixed-effect model. The results from the mixed-effect model are provided in Table 23.

Table 23: Study C-03-32, Reviewer's Mixed-Effect Model with Unstructured Convariance (ITT without Imputation of Missing Data)

	LS mean difference between Nepafenac and vehicle (Nepafenac – vehicle)		P-value for test of |difference| = 0
	Estimate	**Std Err**	
Day 1	-0.3	0.1	<0.0001
Day 3	-0.6	0.1	<0.0001
Day 7	-0.9	0.1	<0.0001
Day 14	-0.6	0.1	<0.0001

5. Percentage of Ocular Pain-Free Patients

Due to the concern that fitting of non-linear mixed-effect model is sensitive to the initial parameter estimates, I performed a sensitivity analysis, using chi-square test to compare the percent of pain-free patients between the two treatment groups at each visit in both ITT and PP populations. The results were consistent with the sponsor's, i.e., the percents of patients with absence of ocular pain were significantly different between the two groups in all post-operative visits, and more patients who received Nepafenac treatment were free of ocular pain than the patients receiving the vehicle treatment at each visit.

Similar to Study C-02-53, I also carried out an analysis including all randomized patients who took at least one dose of study medication and considering those who did not have a post-operative follow-up visit or who did not complete IOL implant surgery as patients with ocular pain. The analysis again obtained the same findings as the sponsor's.

6. Ocular Pain Score

I evaluated the treatment difference in ocular pain score at each visit using two-group t test (Table 24). The treatment differences in all post-operative follow-up visits were statistically significant, and Nepafenac appeared to reduce ocular pain score by at least 25% compared to the vehicle. The results from PP without LOCF were similar to those from ITT with LOCF, and therefore are not presented here.

Table 24: Study C-03-32, Ocular Pain Score by Treatment and Visit (ITT with LOCF)

		Day 1	Day 3	Day 7	Day 14
Nepafenac 0.1%, TID (N=243)	**Mean**	0.2	0.1	0.2	0.1
	SD	0.5	0.4	0.5	0.4
	Min	0	0	0	0
	Max	3	3	4	4
vehicle (N=233)	**Mean**	1.1	1.1	1.3	1.3
	SD	1.2	1.3	1.4	1.5
	Min	0	0	0	0
	Max	4	5	5	5
P-value based on t-test		<0.0001	<0.0001	<0.0001	<0.0001

3.2 Evaluation of Safety

Please refer to the medical officer, Dr. Nevitt's review report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

For Study C-03-32, the sponsor's subgroup analysis for the cure rate showed that there was no statistically significant interaction between treatment and each of the demographics variables (e.g. age, gender, race and iris color), respectively. Meanwhile, I carried out the subgroup analysis for cell score, the percent of ocular pain-free patients, and the ocular pain score as follows:

1. for cell score and ocular pain score at each visit, use ANOVA including treatment, a demographic variable (i.e., age – dichotomized into <65 and >=65 years, gender, race – dichotomized into Caucasian or not, iris color) and treatment by the variable interaction

2. for the percent of ocular pain-free patients at each visit, use logistics regression including treatment, a demographic variable and treatment by the variable interaction

No statistically significant interaction between treatment and the demographics variables was found except that the treatment by iris color interaction on Day 14 (p=0.0335) was significant for cell score. However, further investigation revealed that the significant interaction was quantitative.

For Study C-02-53, no subgroup analysis was done because of the small number of subjects in some subgroup strata.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study C-02-53

1. The sponsor's ITT analysis included patients who received test article and returned for at least one post-surgical follow-up visit. In fact, all randomized patients receiving at least one dose of study medication should be included in the ITT analysis. The exclusion of patients who did not have post-surgical follow-up visit may lead to bias conclusion.

2. For the cell score, the sponsor used LOCF data to fit the mixed-effect model using compound symmetry covariance in the ITT analysis. This may lead to incorrect estimates of the convariance of the parameters, and therefore biased conclusions. The reviewer conducted two sensitivity analyses: the landmark analysis (fitting a linear regression model at each visit individually) using ITT with LOCF, and the mixed-effect model with unstructured convariance using ITT without imputation of missing data. The sensitivity analysis results were consistent with the sponsor's, i.e., the Nepafenac TID group had significantly different means for the cell score from those of the vehicle group at Days 3, 7 and 14.

3. For the percent of cured patients at each visit, the sponsor fitted a logistics regression using data from all visits, and then tested the treatment difference at each visit by comparing the least square (LS) means. The results indicated the cure rates at Days 7 and 14 were statistically significantly different between the two groups and the Nepafenac group had higher proportions of cured patients on both days. However, the sponsor's SAS program for the logistic regression was incorrect. Also, the numbers of cured patients on Days 1 and 3 in each treatment group were small and some of them were even zero. Therefore, the results from logistics regression may not be reliable. The sensitivity analysis using the Fisher's exact test or chi-square test for each visit revealed that the cure rates at Days 3, 7 and 14 were statistically significantly different between the Nepafenac and vehicle groups. Finally, due to the concern that the sponsor-defined ITT population may result in biased conclusions, I performed an additional sensitivity analysis, using all randomized patients who received at least one dose of study medication and considering those who did not have a post-operative visit as "not cured" patients. The Fisher's exact test or chi-square test was utilized to detect the treatment difference at each visit. I got the same results as the first sensitivity analysis.

Study C-03-32

1. Similar to Study C-02-53, the sponsor's defined the ITT population as all randomized patients who received test article, completed IOL implant surgery, and returned for at least one post-surgical follow-up visit. All randomized patients taking at least one dose of study medication should be included in the ITT analysis. The exclusion of patients who did not complete IOL implant surgery or who did not have post-surgical follow-up visit may lead to bias conclusion.

2. For the cell score, the sponsor again used LOCF data to fit the mixed-effect model using compound symmetry covariance in the ITT analysis. This may result in inaccurate estimates of covariance of the parameters, and therefore biased interferences. I again carried out two sensitivity analyses: the landmark analysis using ITT with LOCF, and the mixed-effect model with unstructured convariance using ITT without imputation of missing data. The sensitivity analysis results were consistent with the sponsor's, i.e., Nepafenac TID group had statistically significantly different means for the cell score compared to the vehicle group at all post-operative visits.

3. For the cure rate, the sponsor generated a non-linear mixed-effect model using the data from all visits, and then tested the treatment difference at each visit based on LS means. Fitting a non-linear mixed-effect model is sensitive to the initial values for parameter estimates. It is unclear how the sponsor obtained the starting values. Also, the parameter estimates were heavily based on the data from Days 7 and 14 where there were more cured patients and the differences between the two treatment groups in cure rate were large. As a result, the differences at all post-operative visits were statistically significant even on Day 1 when there was only one cured patient was in the Nepafenac group and no cured patients in vehicle group. The sensitivity analysis using Fisher's exact test or chi-square test performed at each visit demonstrated that there were significant differences in the cure rate on Days 7 and 14 only. Finally, due to the concern about the incorrect definition of the ITT population by the sponsor, I performed an additional sensitivity analysis including all randomized patients who took at least one dose of study medication and treating those who did not have a post-surgical follow-up visit or who did not complete IOL implant surgery as not cured patients. The Fisher's exact test or chi-square test was employed to evaluate the treatment difference at each visit. The results were consistent with the first sensitivity analysis.

5.2 Conclusions and Recommendations

Study C-02-53

1. Nepafenac Suspension, 0.1%, TID group had statistically significantly different means for the cell score from the vehicle group at Days 3, 7 and 14. The difference in mean for the cell score between the Nepafenac Suspension and vehicle groups was -0.2, -0.5, -0.9 and -1.1 at Days 1, 3, 7 and 14, respectively. Thus, when compared to the vehicle, the Nepafenac Suspension, 0.1% TID reduced the mean for the cell score by at least one unit only at Day 14.

2. The proportions of ocular pain-free patients were statistically significantly different between the two study groups at all post-operative visits, with more patients free of ocular pain in the Nepafenac Suspension, 0.1%, TID group.

3. The differences in the cure rates on Days 3, 7 and 14 were statistically significantly different between the two treatment groups, with more cured patients in the Nepafenac Suspension, 0.1%, TID group.

4. The differences in the means for the ocular pain score between the two groups reached statistical significance at all post-operative visits. Furthermore, the Nepafenac Suspension, 0.1%, TID group appeared to reduce the means for the ocular pain by at least 25% compared to the vehicle at all post-operative visits.

Study C-03-32

1. The Nepafenac Suspension, 0.1%, TID group had statistically significantly different means for the cell score compared to the vehicle at all post-operative visits. The difference in mean for the cell score between the Nepafenac Suspension, 0.1%, TID and vehicle groups was -0.3, -0.7, -1.1 and -1.4 on Days 1, 3, 7 and 14, respectively. Nepafenac Suspension, 0.1%, TID reduced the cell score by at least one unit on Days 7 and 14 only.

2. The statistically significantly differences in the percentages of ocular pain-free patients between the two study groups were detected at all post-operative visits, with more pain-free patients in Nepafenac Suspension, 0.1%, TID group at each visit.

3. Nepafenac Suspension, 0.1%, TID had statistically significantly different cure rates compared to vehicle at Days 7 and 14. The sponsor's analysis used non-linear mixed-effect model and the estimates of the model parameters were heavily based on the data from Days 7 and 14. As a result, the differences between Nepafenac and vehicle groups in cure rate on Day 1 was also significant even though there was only one cured patient in the Nepafenac group and no cured patient in the vehicle group on that day. The sensitivity analysis using Fisher's exact test showed that the differences in the cure rates between the two groups at Days 1 and 3 were not significant. Therefore, the results on Days 1 and 3 were inconclusive.

4. The differences in the means for the ocular pain score between the two groups achieved statistical significance at all post-operative visits. Furthermore, the Nepafenac Suspension, 0.1%, TID appeared to reduce the ocular pain by at least 25% compared to the vehicle at all post-operative visits.

6. Appendix

This appendix contains tables of the patient demographics, baseline characteristics and the results for some efficacy endpoints for each study.

6.1 C-02-53

Table 25: Study C-02-53, Patient Demographics (ITT)

	Nepafenac 0.1% QD (N=48)	Nepafenac 0.1% BID (N=50)	Nepafenac 0.1% TID (N=56)	vehicle (N=58)	P-value
Age (years)					0.7748 (a)
Mean	71.4	69.3	70.4	70.3	
SD	9.7	10.7	10.6	8.8	
Min-Max	51 - 89	47 - 86	48 - 91	50 - 90	
Age group					0.9421 (b)
13 – 64 yrs	10 (20.8%)	13 (26.0%)	13 (23.2%)	13 (22.4%)	
>=65 yrs	38 (79.2%)	37 (74.0%)	43 (76.8%)	45 (77.6%)	
Sex					0.1533 (b)
Male	17 (35.4%)	28 (56.0%)	21 (37.5%)	25 (43.1%)	
Female	31 (64.6%)	22 (44.0%)	35 (62.5%)	33 (56.9%)	
Race					0.6204 (c)
Caucasian	35 (72.9%)	42 (84.0%)	46 (82.1%)	45 (77.6%)	
Black	1 (2.1%)	3 (6.0%)	3 (5.4%)	3 (5.2%)	
Asian	1 (2.1%)	1 (2.0%)	0 (0%)	1 (1.7%)	
Other	11 (22.9%)	4 (8.0%)	7 (12.5%)	9 (15.5%)	
Iris Color					0.4868 (c)
Brown	20 (41.7%)	21 (42.0%)	22 (39.3%)	36 (62.1%)	
Hazel	7 (14.6%)	7 (14.0%)	10 (17.9%)	4 (6.9%)	
Green	5 (10.4%)	4 (8.0%)	6 (10.7%)	6 (10.3%)	
Blue	13 (27.1%)	16 (32.0%)	17 (30.4%)	11 (19.0%)	
Gray	3 (6.3%)	2 (4.0%)	1 (1.8%)	1 (1.7%)	
Aqueous Cell Score					0.5078 (a)
Mean	0.0	0.0	0.0	0.0	
SD	0.1	0.1	0.0	0.0	
Min - Max	0 - 1	0 - 1	0 - 0	0 - 0	
Aqueous Flare Score					NA
Mean	0.0	0.0	0.0	0.0	
SD	0.0	0.0	0.0	0.0	
Min - Max	0 - 0	0 - 0	0 - 0	0 - 0	
Ocular Pain Score					0.5078 (a)
Mean	0.0	0.0	0.0	0.0	
SD	0.1	0.1	0.0	0.0	
Min - Max	0 - 1	0 - 1	0 - 0	0 - 0	

Source: CSR-Clinical Study Report for C-95-93, Section 11.2.1, Table 11.2.1.-1 in Vol.4, Module 5 for descriptive statistics for demographics; Section 16.1.9.5 in Vol.5, Module 5 for p-values;

(a) The p-values were based on one-way ANOVA with treatment as factor, using REML.

(b) The p-values were based on Pearson Chi-square test.

(c) The p-values were based on Fisher's exact test.

Table 26: Study C-02-53, Aqueous Flare Scores by Visit (ITT with LOCF)

		Mean	SD	N	Min	Max	LS Means P-Value
Day 1	Nepafenac 0.1% TID	1.0	0.8	56	0	3	0.7497
	vehicle	1.0	0.9	58	0	3	
Day 3	Nepafenac 0.1% TID	0.7	0.9	56	0	3	0.0052
	vehicle	1.1	1.0	58	0	3	
	Nepafenac 0.1% TID	0.4	0.8	56	0	3	<.0001
	vehicle	1.1	1.1	58	0	3	
Day 7	Nepafenac 0.1% TID	0.5	0.9	56	0	3	0.0006
	vehicle	1.1	1.0	58	0	3	
Day 14	Nepafenac 0.1% TID	0.4	0.8	56	0	3	<.0001
	vehicle	1.1	1.1	58	0	3	

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.2.2-1 in Section 11.4.1.2 in Vol. 8, Module 5.
Test=ANOVA, ANOVA P-values are from LS Means treatment effect by day
LS Means P-value reflects comparison of test product to vehicle
Day1-Day14 effect is Repeated Measures ANOVA

Table 27: Study C-02-53, Aqueous Cell Plus Flare Scores by Visit (ITT with LOCF)

		Mean	SD	N	Min	Max	LS Means P-Value
Day 1	Nepafenac 0.1% TID	2.6	1.5	56	0	6	0.3437
	vehicle	2.9	1.5	58	0	7	
Day 3	Nepafenac 0.1% TID	2.1	1.6	56	0	6	0.0019
	vehicle	3.2	1.7	58	0	7	
Day 7	Nepafenac 0.1% TID	1.7	1.8	56	0	6	<.0001
	vehicle	3.2	2.0	58	0	7	
Day 14	Nepafenac 0.1% TID	1.3	1.8	56	0	6	<.0001
	vehicle	3.1	2.2	58	0	7	

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.2.3-1 in Section 11.4.1.2 in Vol. 8, Module 5.
Test=ANOVA, ANOVA P-values are from LS Means treatment effect by day
LS Means P-value reflects comparison of test product to vehicle
Day1-Day14 effect is Repeated Measures ANOVA

Table 28: Study C-02-53, Percent of Patients with Clinically Significant Inflammation by Visit (ITT with LOCF)

		Total Patients	Patients with Clinically Significant Inflammation		LS Means P-Value
			N	%	
Day 1	Nepafenac 0.1% TID	56	16	28.6	0.4960
	vehicle	58	20	34.5	
Day 3	Nepafenac 0.1% TID	56	13	23.2	0.0123
	vehicle	58	26	44.8	
Day 7	Nepafenac 0.1% TID	56	11	19.6	0.0014
	vehicle	58	27	46.6	
Day 14	Nepafenac 0.1% TID	56	8	14.3	<.0001
	vehicle	58	31	53.4	

Source: CSR – Clinical Study Report for C-02-53, Table 11.4.1.2.4-1 in Section 11.4.1.2 in Vol. 8, Module 5.
Test=ANOVA, ANOVA P-values are from LS Means treatment effect by day
LS Means P-value reflects comparison of test product to vehicle
Day1-Day14 effect is Repeated Measures ANOVA

Table 29: Study C-02-53, Percent of Patients Responding to Treatment (Responders) by Visit (ITT with LOCF)

		Total Patients	Responders		LS Means P-Value
			N	%	
Day 1	Nepafenac 0.1% TID	56	12	21.4	0.1783
	vehicle	58	7	12.1	
Day 3	Nepafenac 0.1% TID	56	23	41.1	0.0081
	vehicle	58	11	19.0	
Day 7	Nepafenac 0.1% TID	56	30	53.6	0.0001
	vehicle	58	12	20.7	
Day 14	Nepafenac 0.1% TID	56	37	66.1	0.0002
	vehicle	58	19	32.8	

Source: CSR - Clinical Study Report for C-02-53, Table 11.4.1.2.5-1 in Section 11.4.1.2 in Vol. 8, Module 5.
Test=ANOVA, ANOVA P-values are from LS Means treatment effect by day
LS Means P-value reflects comparison of test product to vehicle
Day1-Day14 effect is Repeated Measures ANOVA

6.2 C-03-32

Table 30: Study C-03-32, Patient Demographics (ITT)

	Nepafenac 0.1% TID (N=243)	vehicle (N=233)	P-value
Age (years)			0.7496 (a)
Mean	70.0	69.8	
SD	9.2	10.0	
Min - Max	41 - 89	27 - 90	
Age group			0.7772 (b)
18 – 64 yrs	59 (24.3%)	54 (23.2%)	
>=65 yrs	184 (75.7%)	179 (76.8%)	
Sex			0.6703 (a)
Male	109 (44.9%)	100 (42.9%)	
Female	134 (55.1%)	133 (57.1%)	
Race			0.8265 (c)
Caucasian	219 (90.1%)	207 (88.8%)	
Black	8 (3.3%)	11 (4.7%)	
Asian	3 (1.2%)	1 (0.4%)	
Hispanic	12 (4.9%)	13 (5.6%)	
Other	1 (0.4%)	1 (0.4%)	
Iris Color			0.7375 (b)
Brown	92 (37.9%)	97 (41.6%)	
Hazel	46 (18.9%)	39 (16.7%)	
Green	20 (8.2%)	13 (5.6%)	
Blue	80 (32.9%)	79 (33.9%)	
Gray	5 (2.1%)	5 (2.1%)	
Aqueous Cell Score			NA
Mean	0.0	0.0	
SD	0.0	0.0	
Min - Max	0 - 0	0 - 0	
Aqueous Flare Score			NA
Mean	0.0	0.0	
SD	0.0	0.0	
Min - Max	0 - 0	0 - 0	
Ocular Pain Score			0.1377 (a)
Mean	0.0	0.0	
SD	0.9	0.2	
Min - Max	0 - 1	0 - 1	

Source: CSR-Clinical Study Report for C-95-93, Section 11.2.1, Table 11.2.1.-1 in Vol.4, Module 5 for descriptive statistics for demographics; Section 16.1.9.5 in Vol.5, Module 5 for p-values;

(a) The p-values were based on one-way ANOVA with treatment as factor.

(b) The p-values were based on Pearson Chi-square test.

(c) The p-values were based on Fisher's exact test.

Table 31: Study C-03-32, Aqueous Flare Score by Treatment and Visit (ITT with LOCF)

		Day 1	Day 3	Day 7	Day 14
Nepafenac 0.1% (N=243)	Mean	0.8	0.6	0.3	0.2
	SD	0.5	0.6	0.5	0.5
	Min	0	0	0	0
	Max	3	3	3	3
Vehicle (N=233)	Mean	1.1	1.2	1.2	1.1
	SD	0.8	0.9	0.9	1.0
	Min	0	0	0	0
	Max	3	3	3	3
P-Value		<0.0001	<0.0001	<0.0001	<0.0001

Source: CSR - Clinical Study Report for Study C-03-32, Table 11.4.1.1.1-3 in Section 11.4.1.1 in Vol. 12, Module 5.
Non-baseline P-values are LS Means by visit
Repeated measures ANOVA main effect of treatment P-value <0.0001
NA = Not applicable

Table 32: Study C-03-32, Aqueous Cell Plus Flare Score by Treatment and Visit (ITT with LOCF)

		Day 1	Day 3	Day 7	Day 14
Nepafenac 0.1% (N=243)	Mean	2.4	1.9	1.3	0.8
	SD	1.0	1.2	1.3	1.4
	Min	0	0	0	0
	Max	6	6	6	6
Vehicle (N=233)	Mean	3.0	3.2	3.4	3.1
	SD	1.2	1.5	1.6	2.0
	Min	1	0	0	0
	Max	7	7	7	7
P-Value		<0.0001	<0.0001	<0.0001	<0.0001

Source: CSR – Clinical Study Report for Study C-03-32, Table 11.4.1.1.1-4 in Section 11.4.1.1 in Vol. 12, Module 5.
Baseline P-value is from T-Test
Non-baseline P-values are LS Means by Visit
Repeated Measures ANOVA Main Effect of Treatment P-value <0.0001

Table 33: Study C-03-32, Cumulative Percent Treatment Failures by Visit (ITT with LOCF)

Treatment	Total N	Day 1		Day 3		Day 7		Day 14	
		N	%	N	%	N	%	N	%
Nepafenac 0.1%	243	11	4.5	15	6.2	19	7.8	20	8.2
vehicle	233	52	22.3	100	42.9	133	57.1	142	60.9
P-Value		<0.0001		<0.0001		<0.0001		<0.0001	

Source: CSR – Clinical Study Report for Study C-03-32, Table 11.4.1.2.2-1 in Section 11.4.1.2 in Vol. 12, Module 5.
NL Mixed Model P-value<0.0001; main effect of treatment
Failure defined as aqueous cell score ≥ 3 or aqueous flare score = 3 or ocular pain score ≥ 4

Table 34: Study C-03-32, Percent of Patients with Clinically Significant Inflammation by Visit (ITT with LOCF)

Treatment	Total N	Day 1		Day 3		Day 7		Day 14	
		N	%	N	%	N	%	N	%
Nepafenac 0.1%	243	21	8.6	18	7.4	18	7.4	20	8.2
vehicle	233	68	29.2	99	42.5	122	52.4	123	52.8
P-Value		<0.0001		<0.0001		<0.0001		<0.0001	

Source: CSR – Clinical Study Report for Study C-03-32, Table 11.4.1.2.1-1 in Section 11.4.1.2 in Vol. 12, Module 5.

NL Mixed Model P-value<0.0001; Main effect of Treatment

Clinically significant inflammation defined as aqueous cell score plus aqueous flare score ≥ 4

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