CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

CLINICAL STUDIES

NDA/BLA Serial Number:	203491/000
Drug Name:	Nepafenac 0.3% Ophthalmic Solution
Indication(s):	Treatment of pain and inflammation associated with cataract surgery
Applicant:	Alcon
Date(s):	Received date: 12/16/2011 PDUFA date: 10/16/2012
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Keywords:

Cell grade, flare grade, pain grade

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1 EXECUTIVE SUMMARY

The drug product reviewed in this NDA is Nepafenac 0.3% for the treatment of inflammation and pain following cataract surgery. This drug's dosage is once a day (QD) for 16 days, starting the day before cataract surgery and ending 14 days after surgery. The test drug has the same active ingredient and same daily dose as approved drug NEVANAC (Nepafenac 0.1% three times a day (TID)) approved in 2005 (NDA 21862).

To support this indication, the Applicant conducted multiple studies: one 20 subjects safety study on healthy subjects and two large pivotal studies, C09055 and C11003. The statistical review focuses on the findings of these two large studies.

Based on the efficacy and safety assessments of this drug from studies C09055 and C11003, we recommend approval of the drug and suggest some changes in the wording of results in the Clinical Studies section in the label. We also make a recommendation on future trial design and endpoints for this indication. First, we summarize the study design. Then, we present the results supporting our recommendation. Finally, we reference our recommendations for the Clinical Studies section of the label for this drug and for future trial design.

The two studies are similar in design but include a different set of treatment groups, different sample sizes and different centers. The two studies are large multicenter, randomized, double masked studies on subjects undergoing cataract surgery. Both studies followed subjects for 14 days after cataract surgery with the same inclusion and exclusion criteria and same schedule for visits. Study C09055 randomized 2120 subjects from 49 sites in the US and 37 sites in Europe with randomization rates of 4:4:1:1 to four treatment groups, two active drugs groups and two vehicle groups. Study C11003 randomized 1342 subjects from 37 sites in the United States with randomization rates of 2:2:1 to three treatment groups, two active drugs groups and one vehicle group. Both studies compared the test drug, Nepafenac 0.3% QD to its vehicle and to an active control comparator. The active control comparator is Nepafenac 0.1% TID (approved drug) in Study C09055 whereas it is Nepafenac 0.1% QD in Study C11003. In addition, Study C09055 included the vehicle of Nepafenac 0.1% TID for assay sensitivity.

Efficacy results for the endpoints of complete resolution of inflammation (primary endpoint) and complete resolution of ocular pain (secondary endpoint) are summarized in Table 1 and Table 2 below. More details on the findings over time are shown in the statistical review in Table 10 to Table 15 and illustrated in Figure 2 to Figure 5. We see in Table 1 that the test drug is superior to vehicle for both resolution of inflammation and resolution of ocular pain with a very large treatment effect. We see in Table 2 that Study C09055 was successful in showing non-inferiority of test drug to NEVANAC for both inflammation resolution and pain resolution at Day 7 and Day 14 visits with a non-inferiority margin of 10%. However, we see in Table 2 that Study C11003 failed to show superiority of the test drug to the lower dose Nepafenac 0.1% QD at Day 7 or Day 14 visits.

We recommend changes in the label and some changes to study design of future trials for this indication. Our proposed Clinical Studies Section of the label is shown in Section 5.4 of the review. In this section, we provide a more accurate description of the endpoints and different numerical results than the Applicant's. Although our conclusions are the same as Applicant's, our numerical results are different due to differences in definition of Intent to Treat population (ITT). ITT is all randomized subjects in our review and it is all randomized subjects who were dispensed drug and had at least one follow-up post surgery in Applicant's report. In Section 5.3 of this review are our recommendations for future trials about randomization's timing, treatment discontinuation versus study discontinuation and choice of endpoints.

Table 1: Inflammation and Ocular Pain Resolution Results of Nepafenac 0.3% versus Vehicle at Day 14 post-surgery

Study	Treatment	Inflammation Resolution	Ocular Pain Resolution
C09055	Nepafenac 0.3% (n/N*)	552/851 (65%)	734/851 (86%)
	Vehicle (n/N*)	67/211 (32%)	98/211 (46%)
	Difference (95% CI)**	33% (26%, 40%)	40% (32%, 47%)
C11003	Nepafenac 0.3% (n/N*)	331/540 (61%)	456/540 (84%)
	Vehicle (n/N*)	63/268 (24%)	101/268 (38%)
	Difference (95% CI)**	38% (31%, 45%)	47% (40%, 54%)

* n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery. Treatment failure is defined as cells score of grade 3 or greater, a flare score of grade 3 or greater, or an ocular pain score of grade 4 or greater.
** Difference is (test drug – vehicle). The 95% confidence interval is derived using asymptotic approximation.

Table 2: Inflammation and Ocular Pain Resolution of Nepafenac 0.3% versus Active Control Comparators at Day 7 and Day 14

Study	Visit	Treatment	Inflammation Resolution	Ocular Pain Resolution
C09055	Day 7	Nepafenac 0.3% (n/N*)	295/851 (35%)	717/851 (84%)
		NEVANAC (n/N*)	330/845 (39%)	733/845 (87%)
		Difference (95% CI)**	4% (0%, 9%)	2% (-1%, 6%)
	Day 14	Nepafenac 0.3% (n/N*)	552/851 (65%)	734/851 (86%)
		NEVANAC (n/N*)	568/845 (67%)	737/845 (87%)
		Difference (95% CI)**	2% (-2%, 7%)	1% (-2%, 4%)
C11003	Day 7	Nepafenac 0.3% (n/N*)	174/540 (32%)	453/540 (84%)
		Nepafenac 0.1% Once Daily (n/N*)	172/534 (32%)	425/534 (80%)
		Difference (95% CI)**	0% (-6%, 6%)	-4% (-9%, 1%)
	Day 14	Nepafenac 0.3% (n/N*)	331/540 (61%)	456/540 (84%)
		Nepafenac 0.1% Once Daily (n/N*)	322/534 (60%)	439/534 (82%)
		Difference (95% CI)**	-1% (-7%, 5%)	-2% (-7%, 2%)

* n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery.
** Difference is (active control – test drug). The 95% confidence interval is derived using asymptotic approximation.

2 INTRODUCTION

This NDA submission is for Nepafenac 0.3% dosed once a day for 16 days with first dosage one day prior to cataract surgery, continuing on the day of surgery, and for 14 days following cataract surgery. The indication sought by applicant is treatment of inflammation and pain after cataract surgery.

In this section, we first provide an overview of the drug development and summarize the main design characteristics of the two pivotal studies supporting this indication. We will also give a reference to the material and data submitted by Applicant in this NDA and used in this statistical review.

Unless specified otherwise, all tables and figures in this review are produced by the reviewer. Differences between the reviewers' results and the Applicant's results (shown in Appendix) are discussed throughout the review.

2.1 Overview

The test drug in this NDA, Nepafenac, is a Non-steroidal anti-inflammatory drug (NSAID). The sought indication is treatment of pain and inflammation following cataract surgery. The proposed dosage of this drug is 0.3% once a day (QD). This dosage is the same daily dose and lower frequency administration than an approved drug for this indication: NEVANAC® (Nepafenac 0.1% three times a day (TID) approved in 2005, NDA 21862).

The clinical development of this drug included one short term safety study and two pivotal trials. The four days of treatment safety study 09-053 is randomized double masked placebo controlled, parallel groups on 20 healthy subjects (12 subjects to test drug and 8 subjects to vehicle). Results from this safety study will not be discussed in this review. This statistical review will focus on the findings in the two large pivotal studies (C09055 and C11003).

The main design features of the two pivotal studies C09055 and C11003 are summarized in Table 3. As we see in this table, studies C09055 and C11003 are randomized, double masked, placebo controlled, parallel groups studies with a treatment period of 16 days on subjects undergoing cataract surgery. Study C09055 was a multinational study with sites in US and Europe (with Europe accounting for 268/2120 (13%) of randomized subjects). In contrast, study C11003 had sites in the US only (with a total of 1342 subjects).

The studies have different treatment groups although they both compare Nepafenac 0.3% (QD) to its vehicle. The primary goal in both studies is to show superiority of the test drug Nepafenac 0.3% (QD) to its vehicle for resolution of inflammation and pain post-surgery. In addition to superiority to vehicle, Study C09055 aimed to show non-inferiority of the proposed drug to the approved drug (Nepafenac 0.1% TID) with a 10% margin for both inflammation and pain resolution. In addition to superiority to vehicle, Study C11003 compared Nepafenac 0.3% (QD) to the lower dose Nepafenac 0.1% (QD) to investigate superiority of the higher dose to the lower dose at day 7 post-surgery.

Table 3: List of Studies Reviewed in this NDA

Studies/Centers /#Subjects randomized*	Phase and Design	Treatment Period	Treatment groups (# of Subjects randomized*)	Study Population
C09055 (65 sites: 49 in the US and 16 in European countries) Randomized: 2120	Phase 3, randomized, double-masked, placebo controlled, parallel groups	16 days**	Nepafenac 0.3% QD (851) Vehicle of 0.3% QD (211) Nepafenac 0.1% TID (845) Vehicle of 0.1% TID (213)	Subjects undergoing cataract surgery
C11003 37 sites in US Total Randomized: 1342	Phase 3, randomized, double-masked, placebo controlled, parallel groups	16 days**	Nepafenac 0.3% QD (540) Nepafenac 0.1% QD (534) Vehicle QD (268)	Subjects undergoing cataract surgery

* This number differs from the safety dataset size reported by applicant in Table 2.5.1-1 in Clinical Overview (module 2). Our number includes the number of all subjects randomized into the study, whereas the applicant reported the numbers in their Intent to Treat Population (ITT) (randomized, had surgery, were dispensed the drug and had at least one follow up post-surgery)

****** First dosage 1 day prior to cataract surgery, continuing on the day of surgery, and for 14 days following cataract surgery

2.2 Data Sources

This NDA submission is electronic. Summaries of clinical studies are at \\cdsesub1\EVSPROD\NDA203491\0000\m2\. Individual clinical reports for this submission and original datasets are at \\cdsesub1\EVSPROD\NDA203491\0000\m5\
The Applicant's proposed label is at \\cdsesub1\EVSPROD\NDA203491\0000\m1\us

Since the data was neither integrated between the two studies nor well documented, a statistics information request was sent to the Applicant prior to filing. The Applicant sent new integrated datasets and documentation in response to this information request, these files are at \\cdsesub1\EVSPROD\NDA203491\0002\m5\datasets

Formatting of the data does not follow SDTM standards. There is no distinction between analysis datasets and tabulation datasets.

3 STATISTICAL EVALUATION

We first discuss data and analysis quality in Subsection 3.1. Then, Subsection 3.2 discusses at length the evaluation of efficacy, the focus of this review. The end of this subsection has the results and conclusions referred to in the Executive Summary. Finally, a short discussion of safety will follow in Subsection 3.3.

3.1 Data and Analysis Quality

We could reproduce the Applicant's findings from the submitted datasets. However, the analyses shown in this review differ slightly with those of the Applicant due to our different definitions of ITT population. Our analyses rely on all randomized subjects, whereas the Applicant's analyses rely on all randomized subjects who were dispensed treatment and attended one post-surgery visit.

One deficiency in the design is that Applicant did not collect any efficacy data on subjects who discontinued treatment due to treatment failure. Applicant did not collect information on whether those discontinuing treatment received rescue medication and what the rescue medication was.

The main datasets used in our analyses are patdem01.xpt, effica01.xpt, dispo01.xpt from \\cdsesub1\EVSPROD\NDA203491\0002\m5\datasets. We also used tf_i01.xpt file in each study from the original data for exploring treatment failure endpoint \\cdsesub1\EVSPROD\NDA203491\0000\m5\

Important identifiers in all integrated datasets for subject, study, treatment and visits are SUBJID01, STUDYI01, TMT.NA01 and VISITN01. Note that SUBJID01 is unique within study but not unique between studies.

Main efficacy results are in variables CELL01, FLARE01, OCULAR01, CELL.C01 for cell score, flare score, pain score and indicator of last observation carried forward (LOCF) imputation in dataset effica01.xpt.

Disposition variables PAT_IT01, EXCL_R01 and REASON01 are indicator for whether subjects are in ITT, reason for exclusion from analysis and reason for discontinuation from the study. They are all in dataset dispo01.xpt.

Demographic variables of age, sex, race and region are in the dataset patdem01.xpt.

In our review, we used statistical software R to produce 95% confidence interval using asymptotic method.

3.2 Evaluation of Efficacy

In this long section, we first describe study design and define the two main endpoints in Subsection 3.2.1. Then, we briefly review statistical methods in Subsection 3.2.2. We review patient disposition and demographic characteristics in Subsection 3.2.3 and show the results in details in Subsection 3.2.4.

3.2.1 Study Design and Endpoints

The two studies C09055 and C11003 have similar designs. They are randomized, double-masked, parallel group studies on subjects undergoing cataract surgery. Randomization was stratified by investigator. Duration of treatment in both studies is 16 days and visits are on the same schedule illustrated in the diagram in Figure 1 Baseline, screening and randomization occurred from 2 days to 6 weeks before surgery. Subjects were instructed to start taking the drug the day before the surgery and continue taking it every day for 14 days after surgery. Safety and efficacy were assessed at four visits post-surgery at day 1, day 3, day 7 and day 14.

The treatment groups and sample sizes assigned to each group in the two studies differ. The primary goal in both studies is to compare Naproxen 0.3% QD to its vehicle for efficacy in treatment for inflammation and pain following cataract surgery. Thus, both of these treatment groups, Naproxen 0.3% QD and its vehicle, were in the two studies. The main difference in design of the two studies is in the choice of active control comparators and sample sizes in each group. Study C09055 compares the test drug to the approved Naproxen 0.1% TID to show non-inferiority. The vehicle of Naproxen 0.1% TID was also included in this study for essay sensitivity. The randomization ratio to the four treatment groups in Study C09055 is 4:4:1:1 with lower sample sizes in the two vehicle groups. Study C11003 compares the test drug to the lower daily dose Naproxen 0.1% QD. The goal of this comparison is to show superiority of the test drug to the lower dose for treatment of inflammation and pain post-surgery. The randomization ratio to the three treatment groups in Study C11003 is 2:2:1 with higher sample sizes in the two vehicle groups.

The inclusion and exclusion criteria were the same in both clinical studies. The inclusion criteria were minimal, subjects are adults (18 years or older) of any race with cataract, who planned to undergo cataract surgery, and who were believed (by investigator) to get an improvement in best corrected visual acuity as a result of the surgery. The cataract surgery is a cataract extraction by phacoemulsification with the implantation of a posterior chamber intraocular lens. The key exclusion criteria in the studies were implemented to ensure that patients had no contraindication for the drug and no inflammation prior to randomization and that they did not receive any anti-inflammatory medication other than the assigned therapy.

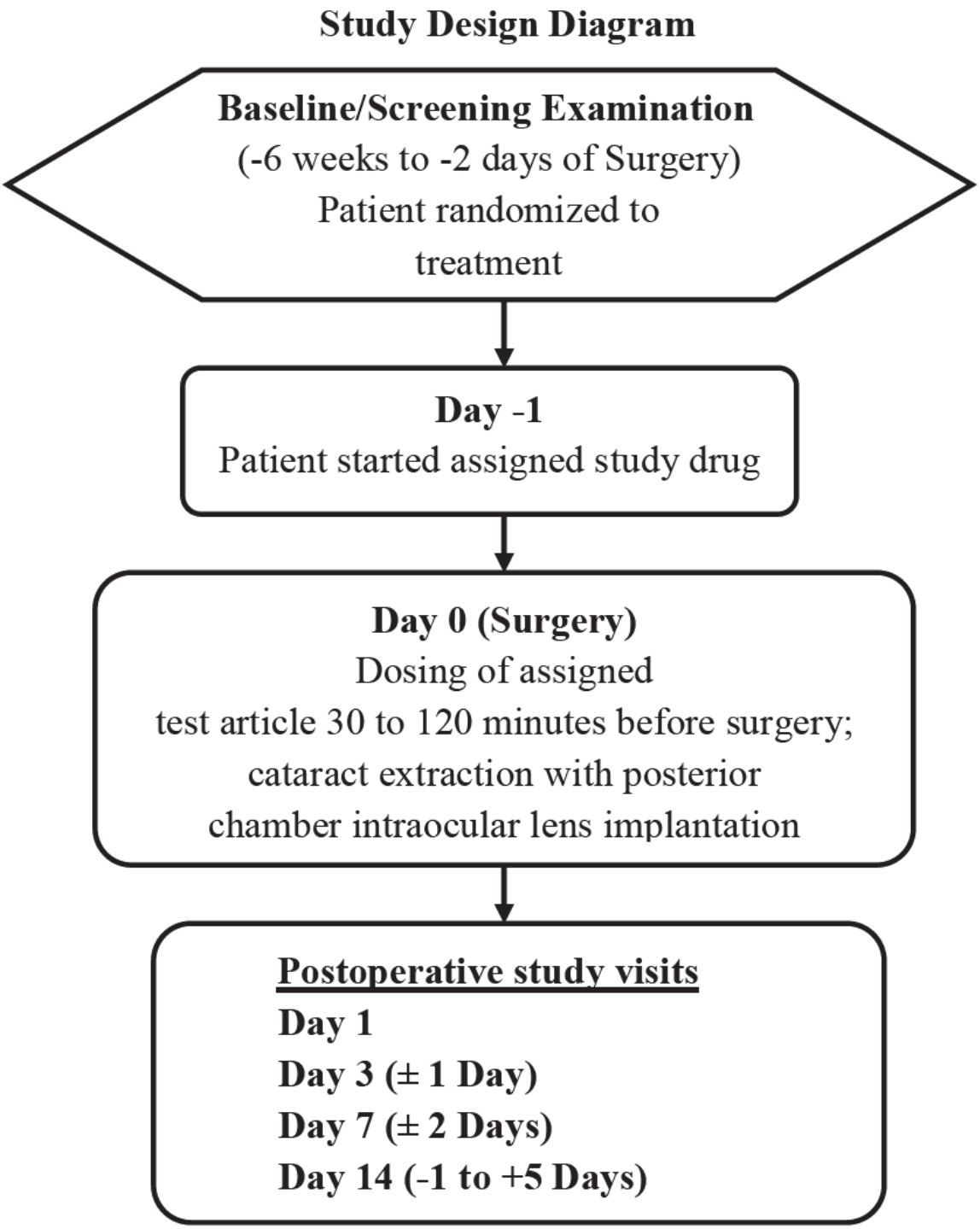

Figure 1: Study Design Diagram
(Source: Applicant's Diagram in Study Report for C09055 and Study Report for C11003)

Endpoints

All primary and secondary endpoints are binary endpoint derived from aqueous cell score and aqueous flare score quantifying inflammation and ocular pain score quantifying ocular pain. The primary endpoint and one secondary endpoint are identical in both studies and collected with similar case report forms and identical grading instructions. Study C11003 included two additional secondary endpoints, which were assessed in Study C09055.

Aqueous cell is scored by investigator in a scale from 0 to 4 quantifying the range of cells observed using slit lamp biomicroscopy (with a slit beam of 0.5mm width and 8mm length at maximum luminance). A grade of 0 is no observed cell; a grade of 1 is 1 to 5 cells; a grade of 2 is 6 to 15 cells; a grade of 3 is 16 to 30 cells; a grade of 4 is greater than 30 cells.

Aqueous flare is scored by investigator in a scale from 0 to 3 quantifying flare using slit lamp biomicroscopy (with a slit beam of 1mm wide beam aimed at the center of the pupil). A grade of 0 is no visible flare when compared with the normal eye; a grade of 1 is mild flare visible against dark papillary background but not visible against iris background; a grade of 2 is moderate flare visible with the slit-lamp beam aimed onto the iris surface as well as the dark papillary background; a grade of 3 is severe or very dense flare.

Ocular pain is also scored by investigator after feedback from each subject in the study in a scale from 0 to 5. Ocular pain is defined as a positive sensation of the eye, including foreign body sensation, stabbing, throbbing or aching. A grade of 0 is no pain; a grade of 1 is a mild sensation of discomfort typical of postoperative ocular surgery; a grade of 2 is a mild tolerable pain; a grade of 3 is moderate and more prolonged aching sufficient to require the use of over the counter analgesics (e.g. acetaminophen/paracetamol); a grade of 4 is moderately severe or more prolonged aching requiring the use of an over the counter analgesic other than acetaminophen/paracetamol; a grade of 5 is severe pain requiring prescription analgesics.

The Applicant's strategy to minimize potential variability in assessment between physicians over time was to instruct physicians to participate in a common training, to require each site to limit the number of doctors performing the grading to 1 to 3 people at each site, and to maintain the same physician grading for each patient over time.

Primary endpoint (in Study C09055 and Study C11003)
The primary endpoint for each subject in both studies is clinical cure of inflammation by day 14. Clinical cure of inflammation was defined as a cell score and flare score of 0 at day 14.

Secondary endpoint in both studies (Study C09055 and C11003)
The main secondary endpoint in both studies is complete resolution of ocular pain (or ocular pain of score zero) at day 14.

Secondary endpoints in study C11003 only
In addition to the primary and secondary endpoints described above, there were two secondary endpoints. Those are the following:

- Clinical success, where clinical success is defined as a cell score less or equal to 1 and flare score of 0

- **Treatment failure**, where treatment failure is defined as cells score of grade 3 or greater, a flare score of grade 3 or greater, or an ocular pain score of grade 4 or greater.

Although treatment failure is used as secondary endpoint in study C11003 only, it was defined in the protocol in both studies and determined whether subjects remained or discontinued from the study (see comment below).

Statistical comment about endpoints
In practice, due to the protocol defined treatment failure and primary analysis, each of these endpoint is in fact a composite endpoint of cell, flare, and pain over time, not only day 14. The protocol in both studies instructed investigators to discontinue from the study all subjects experiencing treatment failure (as defined above) at any post-surgery visit. Thus, once a subject experienced a treatment failure post-surgery, all subsequent cell, flare and pain scores were not collected in the study and were treated as missing values. The intent to treat analysis imputed the last observation to all missing cell, flare and pain scores. Thus, the primary endpoint is in fact a composite endpoint of no treatment failure due to pain or inflammation by day 14 and observed score of zero of aqueous cell and score of zero for aqueous flare by day 14. Similarly, the secondary endpoint of ocular pain resolution is also a composite endpoint of no treatment failure due to pain or inflammation by day 14 and observed score of zero of ocular pain by day 14.

3.2.2 Statistical Methodologies

The endpoints above were the primary and secondary endpoints to determine superiority of the test drug, Nepafenac 0.3% QD, compared to its vehicle in both studies.

Superiority of test drug to Nepafenac 0.1% QD in Study C11003 used complete resolution of inflammation and pain at day 7 (not day 14 as in all other primary analyses comparisons).

In both studies primary statistical analyses of superiority were based upon Cochran-Mantel-Haenszel stratified by investigator. Each test was reported at the 5% significance level, 2-sided.

The test of Non-inferiority of test drug to Nepafenac 0.1% TID in Study C09055 was for both primary and secondary endpoint of pain resolution with non-inferiority margin of 10%. A 95% confidence interval of the difference between the two resolution rates at day 14 using asymptotic approximation is used for this test.

Testing was hierarchical in both studies. Comparison of inflammation and pain resolution to vehicle, as measured by primary and secondary endpoint, is done first before comparison to

active control with the same endpoints. Testing for the primary endpoint of inflammation resolution is done first before testing for the secondary endpoint of pain resolution.

Primary analysis in both studies is on ITT population. This is defined by Applicant as all patients who received study medication, had cataract surgery and returned for at least one scheduled postoperative visit.

Our review considers ITT population as all randomized subjects regardless of post-randomization variables. We will present the results on this population. This disagreement in the definition of what constitutes ITT analysis is the main difference between tables presented in this review and those in the Applicant's study report. See Appendix B for Applicant's results.

Missing values and their handling

As we specified earlier, our definition of ITT population is different from Applicant. In the protocol, the Applicant stated that subjects were discontinued from study if they had not been dispensed the drug before surgery and surgery date could not be rescheduled.[1] Applicant did not identify these subjects in their datasets. The Applicant's ITT population excluded randomized subjects who either weren't dispensed the study drug or didn't have any post-operative data. We included these subjects in our ITT analysis by imputing their outcomes on all endpoints as failure.

As mentioned above with definition of endpoints in the studies, subjects who met the protocol defined treatment failure (see definition above with endpoints) were discontinued from the studies. Subjects were then dispensed therapy (rescue medication) as deemed appropriate by the Investigator. The outcome of these subjects in all endpoints was imputed by Applicant and in our analysis as failure at any visit following their drop out.

Missing values for cell, flare and pain score for subjects with no treatment failure were imputed using Last Observation Carried Forward (LOCF) in the Applicant's analysis and our analysis.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 2120 subjects were enrolled in Study C09055 and randomized to one of four treatment groups: Nepafenac 0.3%, Nepafenac 0.1% TID, Vehicle of Nepafenac 0.3% or Vehicle of Nepafenac 0.1% TID (4:4:1:1). A total of 1342 subjects were enrolled in Study C11003 and

[1] Although surgery scheduling conflict is listed as a possible reason, none of those discontinued from the study reported this reason from the two studies. Discontinuation's reason from randomization to the day 1 post-surgery visit, from Applicant's data and summaries of the two studies, are either not being dispensed the drug or failing to show up at all post-surgery visits.

randomized to one of three treatment groups: Nepafenac 0.3%, Nepafenac 0.1% QD, Vehicle of Nepafenac 0.3% (2:2:1). Summary of subjects who were randomized and treated and those who completed the study or discontinued are shown in Table 4 for Study C09055 and Table 5 for Study C11003.

Table 4: Patient Disposition, Study 09055
(Source: Applicant's Table 10.1-1 in Study C09055 report)

Patient Status	Nepafenac 0.3% N=851 n (%)	NEVANAC N=845 n (%)	Nepafenac Vehicle 0.3% N=211 n (%)	NEVANAC Vehicle N=213 n (%)	Total N=2120 n (%)
Randomized	851 (100.0)	845 (100.0)	211 (100.0)	213 (100.0)	2120 (100.0)
Treated	817 (96.0)	819 (96.9)	200 (94.8)	206 (96.7)	2042 (96.3)
Completed	763 (89.7)	759 (89.8)	110 (52.1)	120 (56.3)	1752 (82.6)
Discontinued	88 (10.3)	86 (10.2)	101 (47.9)	93 (43.7)	368 (17.4)

n is the number of patients for the treatment status
% is calculated as (n/N)*100

Table 5: Patient Disposition, Study C11003
(Source: Applicant's Table 10.1-1 in Study C11003 report)

Patient Status	Nepafenac 0.3% N=540 n (%)	Nepafenac 0.1% N=534 n (%)	Nepafenac Vehicle 0.3% N=268 n (%)	Total N=1342 n (%)
Randomized	540 (100.0)	534 (100.0)	268 (100.0)	1342 (100.0)
Treated	522 (96.7)	506 (94.8)	254 (94.8)	1282 (95.5)
Completed	475 (88.0)	458 (85.8)	121 (45.1)	1054 (78.5)
Discontinued	65 (12.0)	76 (14.2)	147 (54.9)	288 (21.5)

n is the number of patients for the treatment status
% is calculated as (n/N)*100

We see in Table 4 and Table 5 that about 4% of subjects in each group and each study were not treated. These subjects were not dispensed the treatment they were randomized to. We see also that discontinuation rates are high in the vehicle groups reaching about half of randomized subjects in those groups. These discontinuation rates are 4 times as high in vehicle groups as in the active control groups. Discontinuation rate is only 10% in both active control groups in Study C09055 compared to 44% to 48% in the vehicle groups in the same study. Similarly, discontinuation rate is 12%-14% in the active control groups in Study C11003 compared to 55% in the vehicle group in the same study. We further explore reasons for not being treated and reasons for missingness in Table 6 to Table 8.

The reasons for study discontinuation of those excluded from the Applicant's ITT analysis are shown in Table 6 for Study C09055 and Table 7 for Study C11003. Those excluded from the

Applicant's ITT analysis accounted for 4%-8% of those randomized in each treatment group in both studies. The majority of those excluded from the Applicant's ITT analysis, about 80% in Study C09055 and about 70% in Study C11003 were not dispensed medication. In the active control groups, most of the remaining subjects not in the Applicant's ITT analysis were discontinued because of no follow up data due to adverse events. No subjects from the vehicle groups were excluded from the Applicant's ITT analysis due to adverse events.

Table 6: Reasons for Discontinuation for Those Excluded from Applicant's ITT Analysis, Study C09055

Treatments Study C09055		Nepafenac 0.3% QD	Nepafenac Vehicle 0.3%	Nepafenac 0.1% TID	Nepafenac 0.1% Vehicle
All Randomized (N)		851	211	845	214
Excluded from Applicant's ITT (n, n/N)		44 (5%)	14 (7%)	32 (4%)	8 (4%)
Reasons for Discontinuation in Those Excluded from Applicant's ITT					
Not dispensed medication		33	12	26	7
No follow up data	Total	9	2	6	1
	Adverse event	4	0	3	0
	Lost to follow up	1	0	0	0
	Patient's decision	3	0	0	0
	Non-compliance	0	0	0	0
	Protocol Violation	0	0	2	0
	Other	1	2	1	1

Table 7: Reasons for Discontinuation for Subjects Excluded from Applicant's ITT Analysis, Study C11003

Treatments Study C11003		Nepafenac 0.3% QD	Nepafenac Vehicle 0.3%	Nepafenac 0.1% QD
All Randomized (N)		540	268	534
Excluded from Applicant's ITT (n, n/N)		28 (5%)	16 (6%)	41 (8%)
Reasons for Discontinuation in Those Excluded from Applicant's ITT				
Not dispensed medication		18	14	28
No follow up data	Total	10	2	13
	Adverse event	5	0	4
	Lost to follow up	0	0	0
	Patient's decision	0	0	0
	Non-compliance	2	0	2
	Protocol Violation	2	2	7
	Other	1	0	0

Table 8 shows that all of those subjects with missing cell values at day 14 discontinued from the study and their reason for discontinuation was recorded. The rate of missing values is seven to eight folds higher in the vehicle groups (with rates of 39%-49% in different treatment groups) than in the active control groups (with rates of 5%-7%) in both studies. In both studies and in all treatment groups, the most common reason for missingness is treatment failure, the next most common reason is adverse events and the third most common reason is unspecified (category other). However, the contribution of each discontinuation reason to missingness or to all randomized subjects varied depending on whether the treatment group was an active drug or a vehicle. In the vehicle groups, treatment failure was the reason for discontinuation for at least 3 quarters of missing values compared to about half of missing values in the active groups. The rate of discontinuation due to adverse events among all randomized was similar in all treatment groups (1% - 4%). Discontinuation due to adverse events accounted for about a quarter of missing values in the active control groups compared to 6%-11% of missing values in the vehicle groups. Finally, the reason for discontinuation was unspecified for a larger proportion of subjects in study C11003 than in Study C09055 and more in vehicle groups than in active control groups.

Table 8: Reasons for Discontinuation for Subjects with Missing Cell Values* at Day 14

Studies	C09055				C11003		
Treatments	**Nepafenac 0.3%**	**Vehicle Nepafenac 0.3%**	**Nepafenac 0.1% TID**	**Vehicle Nepafenac 0.1% TID**	**Nepafenac 0.1% QD**	**Nepafenac 0.3%**	**Vehicle Nepafenac 0.3%**
Randomized N	851	211	845	213	534	540	268
Missing* M (M/N)	44 (5%)	85 (40%)	51 (6%)	84 (39%)	36 (7%)	38 (7%)	131 (49%)
Reasons For Discontinuation for Those with Missing Cell Measurement* at Day 14							
Treatment Failure	23	67	31	63	19	19	101
Adverse Event	11	9	13	6	7	11	6
Lost to Follow up	0	0	1	0	0	0	0
Patient's decision**	2	2	0	0	1	1	2
Non-compliance	0	0	0	0	1	0	0
Protocol Violation	4	1	3	2	0	0	0
Other	4	6	3	13	7	6	22

*Missing in this table refers to those subjects receiving treatment with at least one observed cell measurement at a post-surgery visit and a missing observation at end of study visit (day 14 post-surgery).
**unrelated to adverse event

Demographic Characteristics

Subject's demographic characteristics in both trials are similar in both studies and in all treatment groups within each study. These characteristics are shown in Table 9. Median age is both studies and all treatment groups is around 70 years of age. More females (56% to 61% of all randomized subjects in each group) were in these studies than males (39% to 45% of all randomized subjects in each group). The large majority of subjects in these studies are white (84% to 87% of randomized subjects in each group). The remaining subjects are Black (7% to 9% of randomized subjects in each group) or Asian (5% to 7% of randomized subjects in each group) with very few subjects in other races. Study C09055 included 13% of randomized subjects from Europe with the remaining subjects from US sites. Study C11003 had all centers in US.

Table 9: Demographic and Geographic Characteristics of Subjects in Each Treatment Group and Study

Studies		C09055				C11003		
Treatments		**Nepafenac 0.3%**	**Vehicle Nepafenac 0.3%**	**Nepafenac 0.1% TID**	**Vehicle of Nepafenac 0.1% TID**	**Nepafenac 0.1% QD**	**Nepafenac 0.3%**	**Vehicle Nepafenac 0.3%**
Randomized* (N)		851	211	845	213	534	540	268
Age	Mean (sd)	69 (9.1)	70 (9.3)	69 (9.3)	69 (9.3)	70 (9)	69 (9.3)	69 (9.5)
	Median (min-max)	70 (32, 89)	71 (38, 92)	69 (20, 90)	69 (38, 90)	70 (21, 91)	70 (35, 92)	71 (27, 94)
Sex n (n/N)	Male	357 (42%)	84 (40%)	369 (44%)	94 (44%)	208 (39%)	242 (45%)	115 (43%)
	Female	490 (58%)	126 (60%)	474 (56%)	119 (56%)	326 (61%)	298 (55%)	153 (57%)
Race n (n/N)	White	739 (87%)	181 (86%)	726 (86%)	183 (86%)	451 (84%)	469 (87%)	231 (86%)
	Black	62 (7%)	19 (9%)	63 (7%)	17 (8%)	40 (7%)	40 (7%)	19 (7%)
	Asian	42 (5%)	10 (5%)	50 (6%)	12 (6%)	38 (7%)	31 (6%)	17 (6%)
	Other**	4 (0%)	0 (0%)	4 (0%)	1 (0%)	5 (1%)	0 (0%)	1 (0%)
Region n (n/N)	US	742 (87%)	184 (87%)	740 (88%)	186 (87%)	534 (100%)	540 (100%)	268 (100%)
	Europe	109 (13%)	27 (13%)	105 (12%)	27 (13%)	0 (0%)	0 (0%)	0 (0%)

* Demographic information is missing for 7 subjects in Study C09055: 4 subjects in treatment group Nepafenac 0.3%, 1 subjects in treatment group Vehicle of Nepafenac 0.1% and 2 subjects in treatment group Nepafenac 0.1% TID.

**Category Other includes Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Multiracial and Other

3.2.4 Results and Conclusions

In this subsection, we first summarize the efficacy results for resolution of inflammation over time, then for resolution of ocular pain over time. We then explore the contribution of the protocol defined treatment failure and the impact of missing values to each of these endpoints

For each outcome and in each study, we first compare the test drug, Nepafenac 0.3% QD to its vehicle. Then, we compare the test drug to the active control in the study. That is, compare

Nepafenac 0.3% QD to Nepafenac 0.1% TID in Study C09055 and compare Nepafenac 0.3% to Nepafenac 0.1% QD in Study C11003.

Response rates over time are summarized in Table 10 for Study C09055 and Table 11 for Study C11003 and illustrated in Figure 2 and Figure 3. Estimates and confidence intervals of treatment effect over time of test drug over vehicle are shown in Table 12. Estimates and confidence intervals of treatment effect over time of test drug over active control comparator are shown in Table 13. Rates of treatment failure and missing cell values over time are summarized in Table 14 for Study C09055 and Table 15 for Study C11003. Treatment failure rates over time are illustrated in Figure 4 and missing rates over time are illustrated in Figure 5.

Resolution of Inflammation

Rates of resolution of inflammation in each treatment group and in each study are shown in Table 10 for Study C09055 and Table 11 for Study C11003 and illustrated in Figure 2. Estimates over time and confidence intervals for difference between test drug and vehicle are shown in Table 12. Estimates over time and confidence intervals for difference between test drug and other active control groups are shown in Table 13.

Pattern of resolution rate over time, shown in Table 10 for Study C09055 and Table 11 for Study C11003 and illustrated in Figure 2, is monotone increasing in all treatments and in both studies. The rate of increase is similar between all active control groups, and similar between all vehicle groups. However, the resolution of inflammation rate increases much more rapidly in the active control groups than in the vehicle groups. Complete separation between resolution of inflammation between active and control groups occur around Day 7 visit and is maintained at Day 14 visit.

Complete separation between active control and vehicle groups doesn't occur until Day 7 and Day 14 visits. The resolution rate at Day 1 visit is (6% to 9%) in different treatment groups in Study C09055 and slightly lower, (2% to 4%), in different treatment groups in Study C11003. This initial difference at Day 1 between the two studies is maintained over time with resolution rates in all treatment groups being slightly higher in Study C09055 than in Study C11003. In Study C09055 at Day 7 visit, the inflammation resolution rate in the active control groups is 35% and 39% and only 18% and 21% in the vehicle groups. In Study C11003 at Day 7 visit, the resolution of inflammation rate in the active control groups is 32% compared to 12% in the vehicle group. At Day 14 visit in Study C09055, the inflammation resolution rate in the active groups reaches 65% and 67% compared to only 32% and 34% in the vehicle groups. At Day 14 visit in Study C11003, the inflammation resolution rate reaches 60% and 61% in the active groups compared to only 24% in the vehicle group.

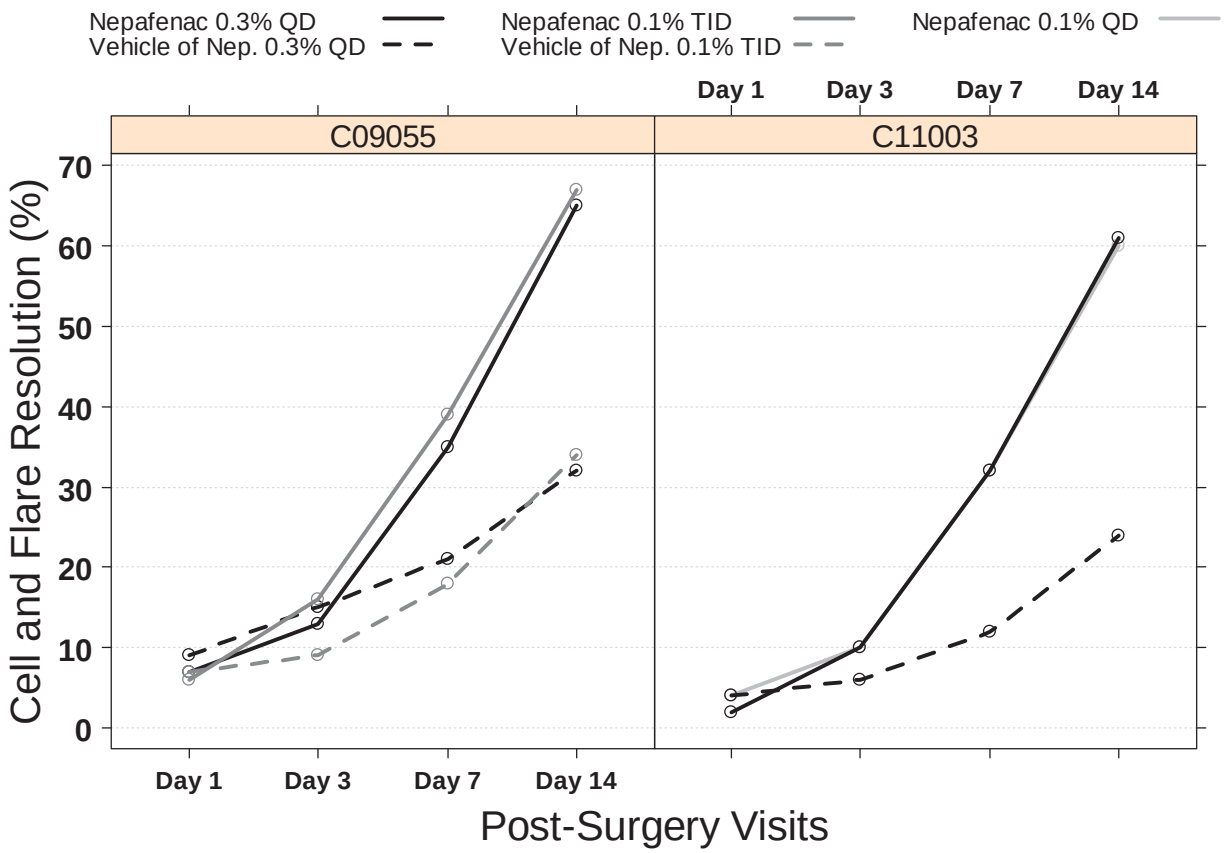

Figure 2: Results on Inflammation Resolution Over Time in Study C09055 and Study C11003 and all Treatment Groups

We see in Table 12 that Napafenac 0.3% QD is significantly superior to its vehicle at Day 7 and Day 14 in both trials. The treatment effect over time is slightly higher in Study C11003 than in Study C09055, and about twice as high at Day 14 than at Day 7 in both studies. At Day 14 (time of assessment of primary endpoint), the treatment effect is 33% with a 95% confidence interval of (26%, 40%) in Study C09055 and the treatment effect is 38% with 95% confidence interval of (31%, 45%) in Study C11003. At Day 7, the treatment effect is 14% with 95% confidence interval of (7%, 20%) in Study C09055 and the treatment effect is 20% with 95% confidence interval of (14%, 26%) in Study C11003.

We see in Table 13 that in Study C09055 Nepafenac 0.3% is non-inferior to Nepafenac 0.1% TID at all time points for resolution of inflammation rate with a non-inferiority margin of 10%. The resolution of inflammation rate in Nepafenac 0.1% TID group is higher at all time points starting at Day 3 visit, but not significantly different, compared to the rate in the test drug. The difference between the two treatment groups is similar over time. At Day 14 (time of assessment of primary endpoint), the difference between resolution of inflammation rate of Nepafenac 0.1% TID and Nepafenac 0.3% QD is 2% with 95% confidence interval of (-2%, 7%). Since the upper bound of the confidence interval is below 10%, the test drug is non-inferior to the approved drug Nepafenac 0.1% TID.

We see in Table 13 that in Study C11003 Nepafenac 0.3% QD fails to show superiority to Nepafenac 0.1% QD at all time points for resolution of inflammation rate. We note that these two treatment groups have nearly identical results for resolution of inflammation rates at every visit.

In both studies and for all treatment groups the results on resolution of inflammation over time are completely driven by resolution of aqueous cell. Cell score and Flare score are associated and as seen in Table 10 and Table 11 nearly all subjects with cell resolution experience a flare resolution. However, flare resolution rates are much higher over time than cell resolution rates over time.

Resolution of Pain

Results on resolution of ocular pain are shown in Table 10 for Study C09055 and Table 11 for Study C11003 and illustrated in Figure 3. Estimates over time and confidence intervals for difference between test drug and vehicle are shown in Table 12. Estimates over time and confidence intervals for difference between test drug and other active control groups are shown in Table 13.

We see in Figure 3 that Pattern of resolution of ocular pain over time is mostly monotone increasing in all treatments and in both studies. The rate of increase is similar between all active control groups, and similar between all vehicle groups. However, the resolution of ocular pain increases much more rapidly in the active control groups than in the vehicle groups. Resolution of ocular pain in active drug groups is large compared to resolution of ocular pain in vehicle groups; it occurs as early as Day 1 post-surgery visit, and is maintained through Day 14 visit.

We see in Table 10 that in Study C09055, vehicle rates of ocular pain resolution start at 38% and 42% at day 1 post surgery and increase to 46% and 54% at day 14 post surgery. Similarly, we see in Table 11 that in study C11003, vehicle rate of ocular pain resolution start at 40% at day 1 post surgery and increases to 38% at day 14 post surgery.

In both studies, resolution rates of ocular pain in active drugs groups is much higher than vehicle groups, starting at Day 1 visit (gap of at least 31%) and increasing gap to above 40% after Day 7 visit. In study C09055, active control rates start at 70% and 73% at day 1 post surgery and increases to 86% and 87% at day 14 post surgery. Similarly, in study C11003, active drug rates start at 70% and 74% at day 1 post surgery and increase to 82% and 84% at day 14 post surgery.

We see in Table 12 that Napafenac 0.3% QD is significantly superior to its vehicle at all post-surgery visits in both trials. The treatment effect over time is similar in Study C11003 than in Study C09055 and similar over time after Day 3 visit. At Day 14 (time of assessment of this endpoint for the comparison to vehicle), the treatment effect is 40% with a 95% confidence interval of (32%, 47%) in Study C09055 and the treatment effect is 47% with 95% confidence interval of (40%, 54%) in Study C11003.

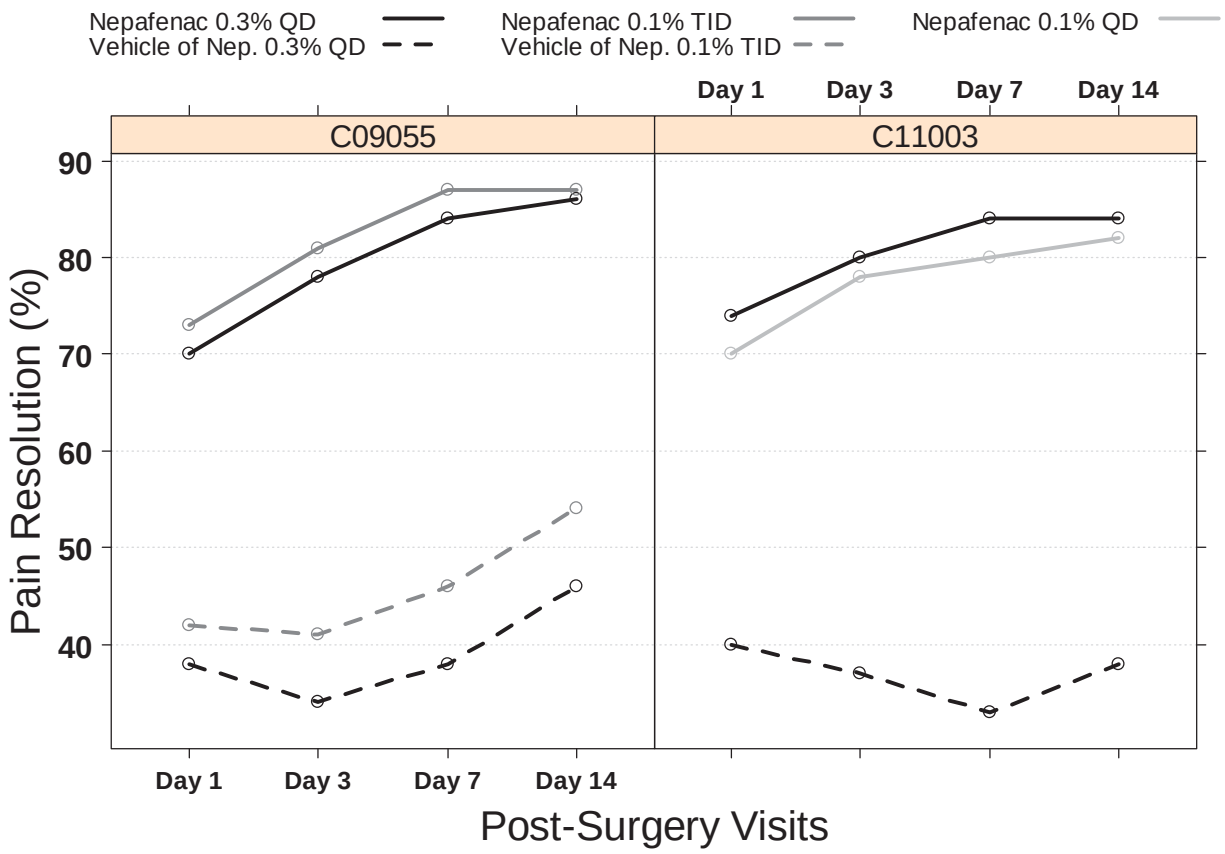

Figure 3: Results on Pain Resolution Over Time in Study C09055 and Study C11003 and all Treatment Groups

We see in Table 13 that in Study C09055, Nepafenac 0.3% is non-inferior to Nepafenac 0.1% TID at all time points for resolution of ocular pain rate with a non-inferiority margin of 10%. The resolution of pain rate in Nepafenac 0.1% TID group is higher at all time points compared to the rate in the test drug. The difference between the two treatment groups is similar over time. At Day 7 (time of assessment of non-inferiority), the difference between resolution of ocular pain rate of Nepafenac 0.1% TID and Nepafenac 0.3% QD is 2% with 95% confidence interval of (-1%, 6%). Since the upper bound of the confidence interval is below 10%, the test drug is non-inferior to the approved drug Nepafenac 0.1% TID.

We see in Table 13 that in Study C11003, Nepafenac 0.3% QD fails to show superiority to Nepafenac 0.1% QD at all time points for resolution rate of ocular pain. However, the resolution rates in Nepafenac 0.3% QD group are higher than those of Nepafenac 0.1% QD group at all time points.

Table 10: Efficacy Results in Study C09055

Visit	Treatment	Total randomized	Resolution of Cell and Flare	Resolution of Pain	Resolution of Cell	Resolution of Flare
		N	n (n/N)	n (n/N)	n (n/N)	n (n/N)
Day 1	Nepafenac 0.3%	851	59 (7%)	592 (70%)	62 (7%)	339 (40%)
	Vehicle Nepafenac 0.3%	211	19 (9%)	81 (38%)	19 (9%)	68 (32%)
	Nepafenac 0.1% TID	845	53 (6%)	614 (73%)	54 (6%)	327 (39%)
	Vehicle Nepafenac 0.1% TID	213	15 (7%)	89 (42%)	15 (7%)	74 (35%)
Day 3	Nepafenac 0.3%	851	113 (13%)	668 (78%)	116 (14%)	480 (56%)
	Vehicle Nepafenac 0.3%	211	32 (15%)	72 (34%)	34 (16%)	78 (37%)
	Nepafenac 0.1% TID	845	133 (16%)	687 (81%)	139 (16%)	483 (57%)
	Vehicle Nepafenac 0.1% TID	213	20 (9%)	87 (41%)	21 (10%)	79 (37%)
Day 7	Nepafenac 0.3%	851	295 (35%)	717 (84%)	301 (35%)	615 (72%)
	Vehicle Nepafenac 0.3%	211	44 (21%)	80 (38%)	48 (23%)	90 (43%)
	Nepafenac 0.1% TID	845	330 (39%)	733 (87%)	336 (40%)	640 (76%)
	Vehicle Nepafenac 0.1% TID	213	38 (18%)	98 (46%)	42 (20%)	87 (41%)
Day 14	Nepafenac 0.3%	851	552 (65%)	734 (86%)	555 (65%)	705 (83%)
	Vehicle Nepafenac 0.3%	211	67 (32%)	98 (46%)	71 (34%)	94 (45%)
	Nepafenac 0.1% TID	845	568 (67%)	737 (87%)	575 (68%)	716 (85%)

	Vehicle Nepafenac 0.1% TID	213	73 (34%)	115 (54%)	73 (34%)	108 (51%)

Table 11: Efficacy Results for Study C11003

Visit	Treatment	Total randomized	Resolution of Cell and Flare	Resolution of Pain	Resolution of Cell	Resolution of Flare
		N	n (n/N)	n (n/N)	n (n/N)	n (n/N)
Day 1	Nepafenac 0.1% QD	534	22 (4%)	372 (70%)	23 (4%)	198 (37%)
	Nepafenac 0.3%	540	12 (2%)	402 (74%)	12 (2%)	227 (42%)
	Nepafenac Vehicle 0.3%	268	10 (4%)	108 (40%)	10 (4%)	85 (32%)
Day 3	Nepafenac 0.1% QD	534	56 (10%)	417 (78%)	59 (11%)	294 (55%)
	Nepafenac 0.3%	540	53 (10%)	431 (80%)	54 (10%)	310 (57%)
	Nepafenac Vehicle 0.3%	268	17 (6%)	100 (37%)	17 (6%)	93 (35%)
Day 7	Nepafenac 0.1% QD	534	172 (32%)	425 (80%)	177 (33%)	362 (68%)
	Nepafenac 0.3%	540	174 (32%)	453 (84%)	182 (34%)	408 (76%)
	Nepafenac Vehicle 0.3%	268	33 (12%)	89 (33%)	35 (13%)	98 (37%)
Day 14	Nepafenac 0.1% QD	534	322 (60%)	439 (82%)	325 (61%)	423 (79%)
	Nepafenac 0.3%	540	331 (61%)	456 (84%)	333 (62%)	454 (84%)
	Nepafenac Vehicle 0.3%	268	63 (24%)	101 (38%)	65 (24%)	107 (40%)

Table 12: Difference in Resolution of Inflammation and Resolution of Ocular Pain Between Nepafenac 0.3% and Vehicle Over Time in Each Study

Study	Visit	Difference (95% CI)*	
		Resolution of Inflammation	Resolution of Ocular Pain
C09055	Day 1	-2% (-7%, 2%)	31% (24%, 39%)
	Day 3	-2% (-8%, 4%)	44% (37%, 52%)
	Day 7	14% (7%, 20%)	46% (39%, 54%)
	Day 14	33% (26%, 40%)	40% (32%, 47%)
C11003	Day 1	-2% (-4%, 1%)	34% (27%, 41%)
	Day 3	3% (-1%, 8%)	43% (36%, 49%)
	Day 7	20% (14%, 26%)	51% (44%, 57%)
	Day 14	38% (31%, 45%)	47% (40%, 54%)

* Difference is for Nepafenac 0.3% QD – Vehicle. So, a positive value is in favor of test drug. 95% CI was computed using asymptotic method.

Table 13: Difference in Resolution of Inflammation and Resolution of Ocular Pain Between Nepafenac 0.3% and Active Control Over Time in Each Study

Study	Visit	Difference (95% CI)*	
		Resolution of Inflammation	Resolution of Ocular Pain
C09055 Active control is Nepafenac 0.1% TID	Day 1	-1% (-3%, 2%)	3% (-1%, 8%)
	Day 3	2% (-1%, 6%)	3% (-1%, 7%)
	Day 7	4% (0%, 9%)	2% (-1%, 6%)
	Day 14	2% (-2%, 7%)	1% (-2%, 4%)
C11003 Active control is Nepafenac 0.1% QD	Day 1	2% (0%, 4%)	-5% (-10%, 1%)
	Day 3	1% (-3%, 4%)	-2% (-7%, 3%)
	Day 7	0% (-6%, 6%)	-4% (-9%, 1%)
	Day 14	-1% (-7%, 5%)	-2% (-7%, 2%)

* Difference is for Active Control - Nepafenac 0.3% QD. So, a negative value is in favor of test drug and a positive value is in favor of the active control drug. The 95% CI is the 95% Confidence interval computed using asymptotic method. If the upper bound of the confidence interval is below 10%, then the test drug is non-inferior to the active control using an NI margin of 10%.

Treatment Failure and Missingness

As we have discussed in Subsection 3.2.1, the endpoint of inflammation resolution and the endpoint of pain resolution are composite endpoints affected by missing values and treatment failure. As we saw in Subsection 3.2.3, the most common listed reason for missingness is treatment failure. We discuss in this subsection, the pattern of treatment failure and missingness

over time since these will affect the outcome. Those rates are shown over time in Table 14 for Study C09055 and Table 15 for Study C11003 and illustrated in Figure 4 for treatment failure rates and Figure 5 for missing value rates.

The pattern of treatment failure is shown in Figure 4. In both studies, treatment failure rates are slightly higher in the vehicle groups than in the active drug groups at Day 1, but they increase dramatically by the next visit (Day 3). At Day 7 visit in the vehicle groups, there is a large increase in Study C11003 and a more modest increase in Study C09055. The rates plateau from Day 7 to Day 14 visit.

In these two studies, treatment failures at a given visit imply missing values at the next visit. We see in Figure 5, Table 14, and Table 15 that rates of missing values are mostly the cumulative treatment failure rates over time.

What we can deduce from these rates is that the high treatment effect in resolution of inflammation and resolution of ocular pain is mostly driven by high treatment effect on treatment failure. By in large the cell score used at Day 14 visit in vehicle groups are those cell score observed at Day 3 or Day 7 visits whereas most cell score used at Day 14 in active control groups are those actually observed on Day 14 visit.

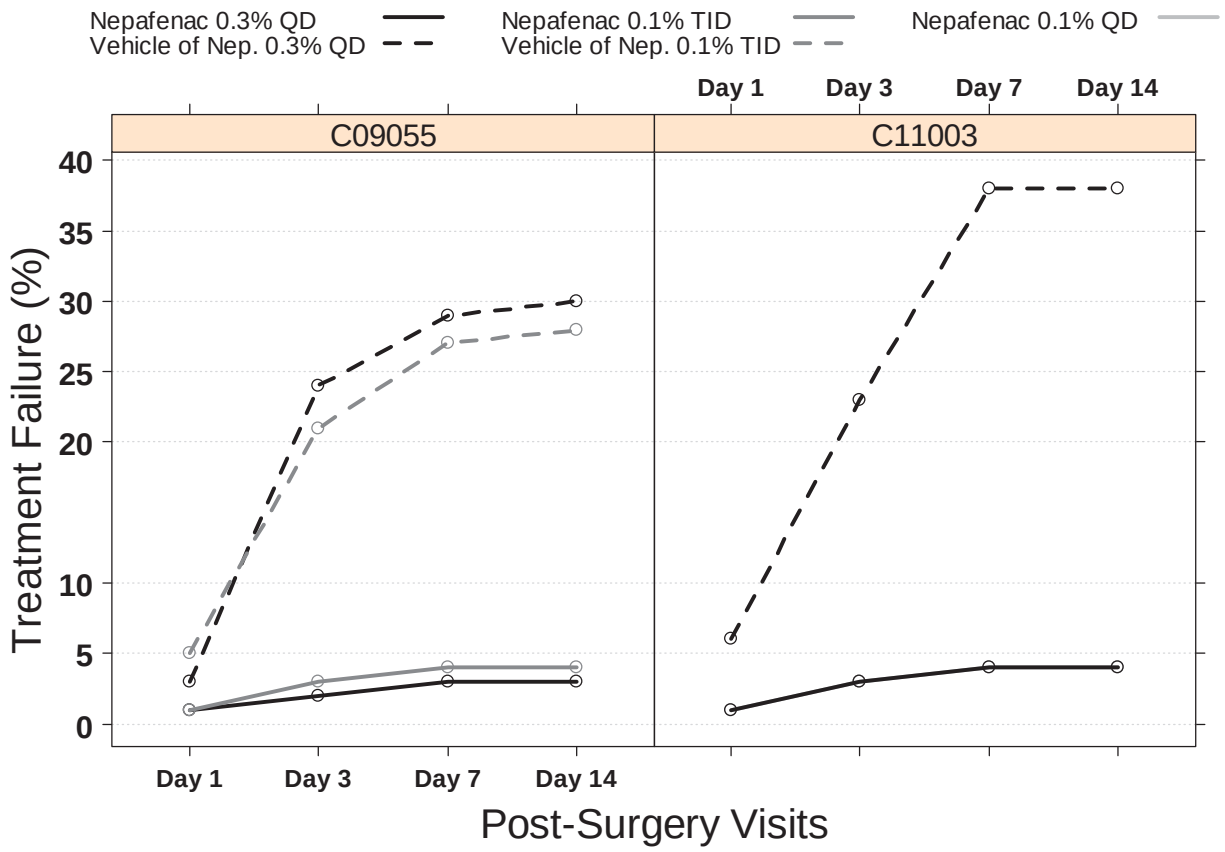

Figure 4: Treatment failure Over Time in Study C09055 and Study C11003 and all Treatment Groups

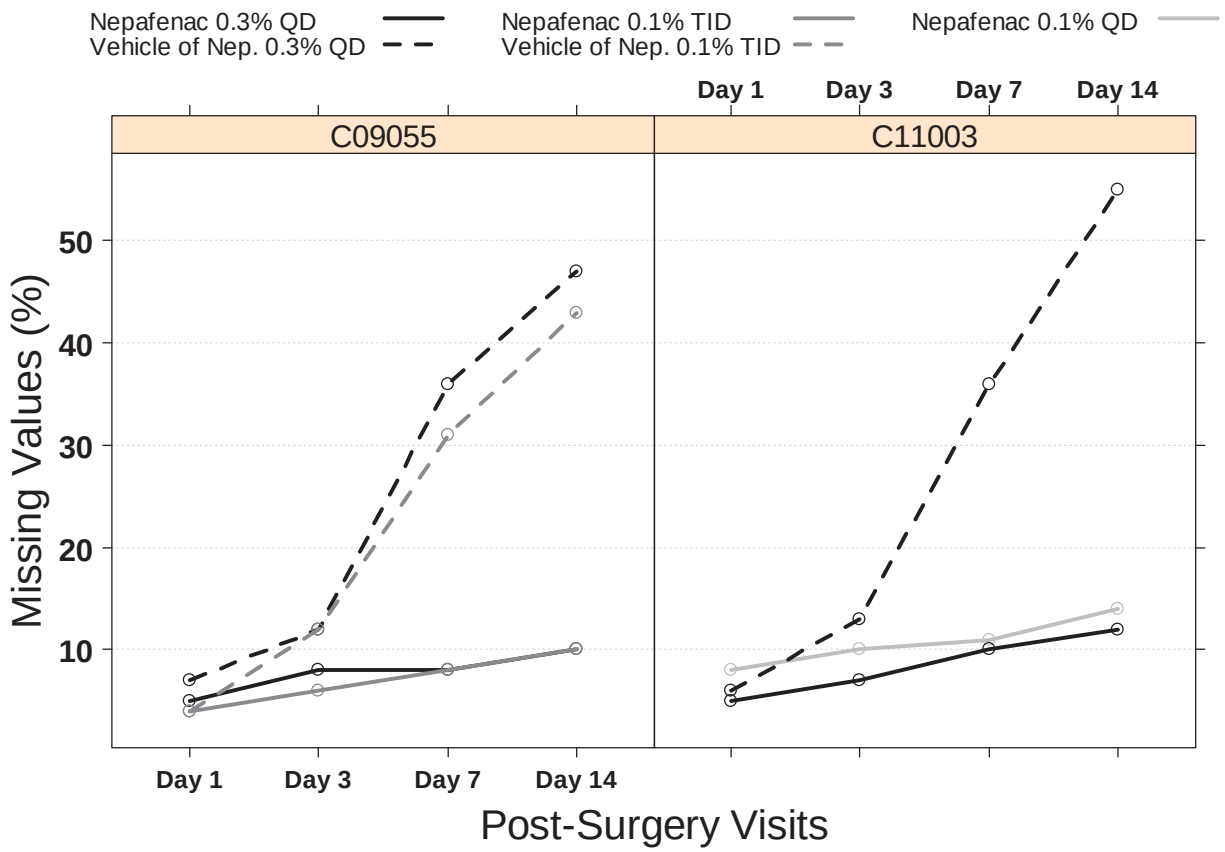

Figure 5: Missing Values on Acqueous Cell Over Time in Study C09055 and Study C11003 and all Treatment Groups

Table 14: Treatment Failure and Missing Values Over Time, Study C09055

Visit	Treatment	Total*	Treatment Failure	Missing
		N	n (n/N)	n (n/N)
Day 1	Nepafenac 0.3%	851	8 (1%)	44 (5%)
	Vehicle Nepafenac 0.3%	211	7 (3%)	15 (7%)
	Nepafenac 0.1% TID	845	12 (1%)	32 (4%)
	Vehicle Nepafenac 0.1% TID	213	11 (5%)	8 (4%)
Day 3	Nepafenac 0.3%	851	25 (3%)	64 (8%)
	Vehicle Nepafenac 0.3%	211	64 (30%)	26 (12%)
	Nepafenac 0.1% TID	845	36 (4%)	52 (6%)
	Vehicle Nepafenac 0.1% TID	213	59 (28%)	26 (12%)
Day 7	Nepafenac 0.3%	851	15 (2%)	71 (8%)
	Vehicle Nepafenac 0.3%	211	51 (24%)	76 (36%)
	Nepafenac 0.1% TID	845	25 (3%)	69 (8%)
	Vehicle Nepafenac 0.1% TID	213	45 (21%)	67 (31%)
Day 14	Nepafenac 0.3%	851	23 (3%)	88 (10%)
	Vehicle Nepafenac 0.3%	211	62 (29%)	99 (47%)
	Nepafenac 0.1% TID	845	35 (4%)	83 (10%)
	Vehicle Nepafenac 0.1% TID	213	58 (27%)	92 (43%)

Table 15: Treatment Failure and Missing Values Over Time, Study C11003

Visit	Treatment	Total*	Treatment Failure	Missing
		N	n (n/N)	n (n/N)
Day 1	Nepafenac 0.1% QD	534	5 (1%)	41 (8%)
	Nepafenac 0.3%	540	5 (1%)	28 (5%)
	Nepafenac Vehicle 0.3%	268	16 (6%)	16 (6%)
Day 3	Nepafenac 0.1% QD	534	22 (4%)	52 (10%)
	Nepafenac 0.3%	540	23 (4%)	38 (7%)
	Nepafenac Vehicle 0.3%	268	102 (38%)	35 (13%)
Day 7	Nepafenac 0.1% QD	534	14 (3%)	61 (11%)
	Nepafenac 0.3%	540	14 (3%)	55 (10%)
	Nepafenac Vehicle 0.3%	268	62 (23%)	97 (36%)
Day 14	Nepafenac 0.1% QD	534	22 (4%)	77 (14%)
	Nepafenac 0.3%	540	22 (4%)	66 (12%)
	Nepafenac Vehicle 0.3%	268	101 (38%)	147 (55%)

3.3 Evaluation of Safety

There are no safety issues with these drugs. We refer to the clinical review of this application for details.

We copied in this section some of the Applicant's tables for treatment related or emergent adverse events from each study report, they are shown in Table 16 to Table 18. We see that there was less than 3% incidence of treatment emergent adverse events such as headache (1% to 2.7% across treatments in both studies) and intraocular pressure increase (0% to 1% across treatments in both studies). The incidence of treatment related adverse events is very low with no subject or only one subject per treatment reporting these adverse events. These treatment-related adverse events are identified as eye pain and hypersensitivity in Study C09055 and eyelid oedema, punctate karatitis and foreign body sensation in the eye in Study C11003. There is no clear dose-response relationship to any of these adverse events.

Table 16: Summary of Treatment-Emergent Adverse Events
(Source: Applicant's Table 12.2.1.1 in Study C09055 Study Report)

	Nepafenac 0.3%		NEVANAC		Nepafenac 0.3% Vehicle		NEVANAC Vehicle	
	N = 817		N = 819		N = 201		N = 205	
Adverse Event Category	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Deaths	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**	**0**	**0.0**
Patients experiencing nonfatal serious adverse events[a]	**7**	**0.9**	**3**	**0.4**	**0**	**0.0**	**0**	**0.0**
Patients discontinued due to an adverse event	**15**	**1.8**	**17**	**2.1**	**9**	**4.5**	**6**	**2.9**
Discontinued due to non-fatal serious adverse events	2	0.2	2	0.2	0	0.0	0	0.0
Discontinued due to nonserious adverse events	13	1.6	15	1.8	9	4.5	6	2.9
Treatment-related	1	0.1	0	0.0	0	0.0	0	0.0
Not related to treatment	12	1.5	15	1.8	9	4.5	6	2.9
Patients with at least 1 treatment-emergent adverse event (related and not related combined)	99	12.1	82	10.0	39	19.4	33	16.1
Most frequent treatment-emergent adverse events (incidence of 1% or greater in active treatment groups)								
Headache	22	2.7	13	1.6	3	1.5	3	1.5
Intraocular pressure increased	8	1.0	7	0.9	0	0.0	0	0.0
Patients with at least 1 treatment-emergent adverse event related to treatment (ADR; adverse drug reaction)								
Eye pain	1	0.1	0	0.0	0	0.0	1	0.5
Hypersensitivity	1	0.1	0	0.0	0	0.0	0	0.0

[a]All nonfatal serious adverse events were assessed as unrelated to the use test article

Table 17: Overall Frequency and Incidence of Adverse Events Occurring at Rates Greater Than or Equal to 1.0%
(Source: Applicant's Table 14.3.1.5.-1 in Study C11003 Report)

	Nepafenac 0.3% N=522		Nepafenac 0.1% N=506		Nepafenac Vehicle 0.3% N=254	
Coded Adverse Event	**N**	**%**	**N**	**%**	**N**	**%**
Investigations						
Intraocular pressure increased	7	1.3	1	0.2	1	0.4
Nervous system disorders						
Headache	5	1.0	6	1.2	2	0.8

Coded adverse event = MedDRA Preferred Term (version 13.0) presented by System Organ Class.

Table 18: Overall Frequency and Incidence of Treatment-Related Adverse Events
(Source: Applicant's Table 14.3.1.6.-1 in Study C11003 Report)

	Nepafenac 0.3% N=522		Nepafenac 0.1% N=506		Nepafenac Vehicle 0.3% N=254	
Coded Adverse Event	**N**	**%**	**N**	**%**	**N**	**%**
Related						
Eye disorders						
Eyelid oedema					1	0.4
Foreign body sensation in eyes					1	0.4
Punctate keratitis	1	0.2				

Coded adverse event = MedDRA Preferred Term (version 13.0) presented by System Organ Class.
Related (R) = Event was assessed as related to the use of test article
Not Related (NR) = Event was assessed as unrelated to the use of test article

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

We review the usual subgroups of gender, race, age and geographic region in this Section.

4.1 Gender, Race, Age, and Geographic Region

The treatment effect for both endpoints of inflammation and pain is consistent in all subgroups by gender, race, age and geographic region. Results are illustrated in the forestplots in Figure 6-Figure 9 and shown in Table 21 to Table 23 in Appendix A.

Note that in the forestplot figures, we grouped age in two different ways. One way (age < 65 and age ≥ 65) is as the Applicant. The other way is our own grouping of age into quartiles across two studies, to have approximately equal size groups. Those quartiles are (<64, 64-69, 70-75, and > 75).
In the forest plots, the confidence intervals are Wilson's confidence interval for difference in proportions

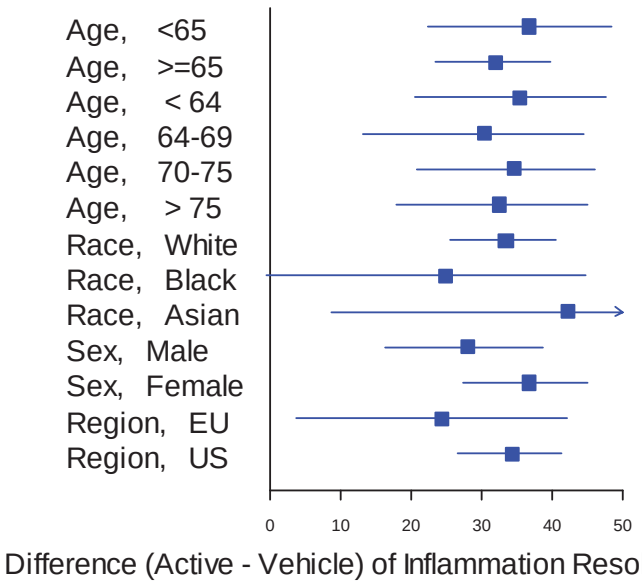

Figure 6: Forest Plot for Treatment Effect on Inflammation Resolution in Different Subgroups, Study C09055

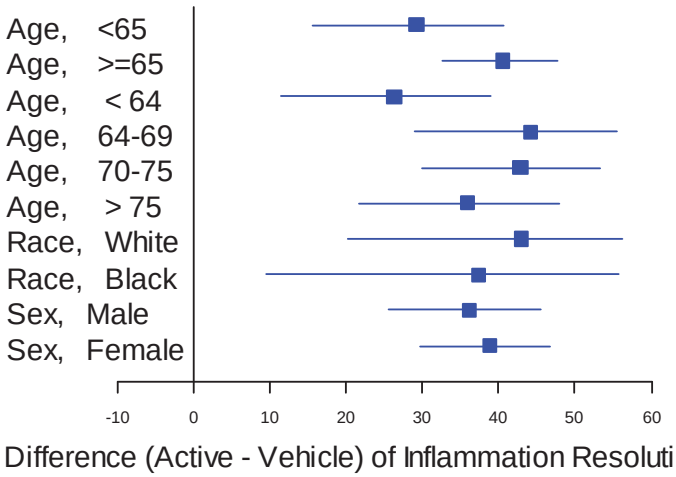

Figure 7: Forest Plot for Treatment Effect on Inflammation Resolution in Different Subgroups, Study C11003

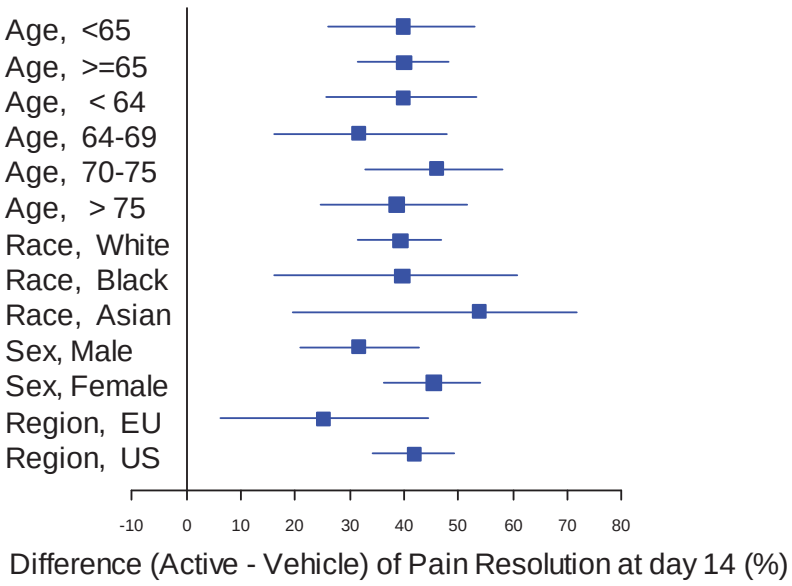

Figure 8: Forest Plot for Treatment Effect on Pain Resolution in Different Subgroups, Study C09055

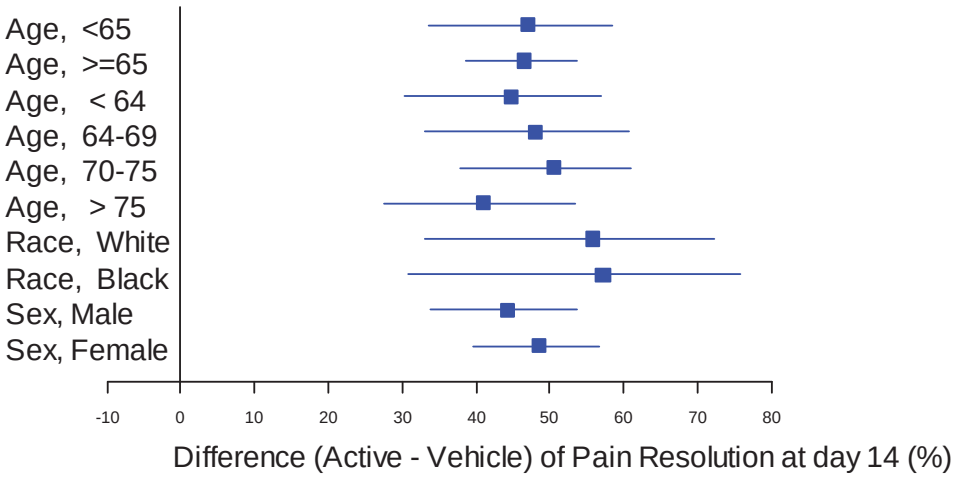

Figure 9: Forest Plot for Treatment Effect on Pain Resolution in Different Subgroups, Study C11003

5 SUMMARY AND CONCLUSIONS

Since there are no main safety issues with this NDA, our summary and conclusions are derived from the efficacy profile of this drug.

5.1 Statistical Issues

We have two main statistical issues, one related to the design of the studies and the other related to the analysis of results from these studies. The first issue related to design is that for the Applicant, discontinuation from treatment meant discontinuation from the study. Thus, those subjects who discontinued drug had missing values at following visits. The second issue is that the Applicant did not include in their intent to treat analysis all randomized subjects.

5.2 Collective Evidence

There are three main conclusions. First, the test drug Nepafenac 0.3% QD is effective against vehicle for treatment of inflammation and pain following cataract surgery as shown in two adequate and well controlled trials. Second, the test drug is non-inferior to Nepafenac 0.1% TID for resolution of inflammation and for resolution of pain using a non-inferiority margin of 10% as shown in Study C09055. Finally, Study C11003 failed to show superiority of the test drug to Nepafenac 0.1% QD.

5.3 Conclusions and Recommendations

We recommend approval of the drug Nepafenac 0.3% QD based on the comparison of this drug to its vehicle in the two trials. Efficacy of this drug compared to vehicle is large and very clear.

There is no clear advantage of this drug compared to the other two active control drugs. We believe that a case could be made by Applicant to approve the lower dose Nepafenac 0.1% QD based on the results of this NDA and the dose ranging study for NEVANAC's (NDA 21862).

Note that the two statistical issues mentioned above do not change our main conclusions. We explain why in the following paragraph.

As we explain in details in the review, the first issue impacts our understanding of what the primary endpoint and the secondary endpoint are. Although the primary endpoint is defined as complete resolution of cell and flare at day 14, it is in fact a composite of cell score, flare score and pain score up to day 14. Similarly the secondary endpoint of complete resolution of ocular pain is also a composite endpoint of cell score, flare score and pain score up to day 14. Our exploratory analyses show that these composite endpoints are still meaningful to compare the treatment groups. Although there are many more dropouts in the vehicle groups than in the active control groups, our exploratory analyses in this review show that treatment failure could explain this differential drop out. So, although we would still prefer Applicant to record what the cell score and flare score for those receiving rescue medication or experiencing an adverse event is,

these findings would only complete our understanding of inflammation and pain process over time after ocular surgery.

For the second issue on definition of intent to treat, we simply presented in our review our own analysis on all randomized subjects treating those who were not dispensed drug or didn't have any post-operative data as failure. We get similar estimates of treatment effects than in the Applicant's analyses shown in Appendix B.

We recommend the following for future trials in this indication: (1) Subjects who discontinue taking the drugs in the clinical trial should remain in the study and have efficacy and safety outcome measured at scheduled visits; (2) ITT analysis should include all randomized subjects who have cataract surgery, regardless of whether or not they were dispensed the drug or had post-operative data. To minimize dispensing errors, the pre-surgery visit can occur earlier than in this trial (screening in this trial was 2 days to 6 weeks before surgery). (3) For comparison to vehicle groups, treatment failure is an important endpoint and should be included at least as a secondary endpoint. The main driving element of the difference in treatment effect between active and vehicle groups was the high rate of treatment failure in the vehicle groups compared to the active drug groups. Thus, analyzing treatment failure endpoint along with complete resolution can provide a better picture of study results than complete resolution alone.

5.4 Labeling Recommendations

Our recommended changes to the label use the numbers from our analyses and give a more accurate definition of the primary endpoints. We propose two different versions. The first version does not include comparisons to other active controls in the studies whereas the second version includes comparisons to other active controls in the studies. We first show the currently proposed language from applicant and present our two versions.

Clinical Studies Section proposed by Applicant

(b) (4)

Clinical Study Section Proposed by Reviewer, Excluding Results on active control comparator

In two double masked, randomized clinical trials in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, TRADENAME demonstrated superior clinical efficacy compared to its vehicle in treating postoperative inflammation and pain. Details on the results from the two studies and definition of resolution of inflammation and resolution of ocular pain are shown in Table 1.

Treatment effect over vehicle for resolution of ocular pain occurred as early as day 1 post-surgery. Treatment effect over vehicle for resolution of inflammation was significantly better than vehicle in both studies at day 7 and day 14 post-surgery.

Table 1: Inflammation and Ocular Pain Resolution Results of Nepafenac 0.3% versus Vehicle at Day 14 post-surgery

Studies	Treatment	Inflammation Resolution[3]	Ocular Pain Resolution[4]
Study 1	TRADENAME (n/N) [1]	552/851 (65%)	734/851 (86%)
	Vehicle (n/N) [1]	67/211 (32%)	98/211 (46%)
	Difference (95% CI) [2]	33% (26%, 40%)	40% (32%, 47%)
Study 2	TRADENAME (n/N) [1]	331/540 (61%)	456/540 (84%)
	Vehicle (n/N) [1]	63/268 (24%)	101/268 (38%)
	Difference (95% CI) [2]	38% (31%, 45%)	47% (40%, 54%)

[1] n/N is the ratio of those with no treatment failure prior to day 14 post-surgery visit and complete resolution by day 14 post-surgery visit over all randomized subjects prior to cataract surgery.

[2] Difference is (test drug – vehicle). The 95% confidence interval is derived using asymptotic approximation.

[3] Inflammation resolution at day 14 is no observed cell and no observed flare and no treatment failure by day 14 post-surgery. Treatment failure is defined as having more than 16 cells, severe or very dense flare, or moderate to ocular pain requiring the use of over the counter or prescription analgesics.

[4] Pain resolution at day 14 is no observed pain by day 14 and no treatment failure prior to day 14 post-surgery. Treatment failure is defined as having more than 16 cells, severe or very dense flare, or moderate to ocular pain requiring the use of over the counter or prescription analgesics.

Clinical Studies Section Proposed by Reviewer, Including Results about Active Controls

In two double masked, randomized clinical trials in which patients were dosed daily beginning one day prior to cataract surgery, continued on the day of surgery and for the first two weeks of the postoperative period, TRADENAME demonstrated superior clinical efficacy compared to its vehicle in treating postoperative inflammation and pain. TRADENAME demonstrated non-inferiority to NEVANAC in one study and failed to demonstrate superiority to Nepafenac 0.1% QD in another study.

Details on the results from the two studies are shown in Table 1 and Table 2. In both tables, efficacy was measured by difference in rates of inflammation resolution and difference in rates of ocular pain resolution. Inflammation resolution at a given post-surgery visit is no observed cell and no observed flare by this visit and no treatment failure prior to this visit post-surgery. Pain resolution at a given post-surgery visit is no observed pain by this visit and no treatment failure prior to this visit. Treatment failure is defined as having more than 16 cells, severe or very dense flare, or moderate to ocular pain requiring the use of over the counter or prescription analgesics.

Treatment effect over vehicle for resolution of ocular pain occurred as early as day 1 post-surgery. Treatment effect over vehicle for resolution of inflammation was significantly better than vehicle in both studies at day 7 and day 14 post-surgery.

Table 1: Inflammation and Ocular Pain Resolution Results of Nepafenac 0.3% versus Vehicle at Day 14 post-surgery

Studies	Treatment	Inflammation Resolution	Ocular Pain Resolution
Study 1	TRADENAME (n/N) (1)	552/851 (65%)	734/851 (86%)
	Vehicle (n/N) (1)	67/211 (32%)	98/211 (46%)
	Difference (95% CI) (2)	33% (26%, 40%)	40% (32%, 47%)
Study 2	TRADENAME (n/N) (1)	331/540 (61%)	456/540 (84%)
	Vehicle (n/N) (1)	63/268 (24%)	101/268 (38%)
	Difference (95% CI) (2)	38% (31%, 45%)	47% (40%, 54%)

(1) n/N is the ratio of those with no treatment failure prior to day 14 post-surgery visit and complete resolution by day 14 post-surgery visit over all randomized subjects prior to cataract surgery.

(2) Difference is (test drug – vehicle). The 95% confidence interval is derived using asymptotic approximation.

Table 2: Inflammation and Ocular Pain Resolution of Nepafenac 0.3% versus Active Control Comparators at Day 7 and Day 14

Studies	Visit	Treatment	Inflammation Resolution	Ocular Pain Resolution
Study 1	Day 7	TRADENAME (n/N) (1)	295/851 (35%)	717/851 (84%)
		NEVANAC (n/N) (1)	330/845 (39%)	733/845 (87%)
		Difference (95% CI) (2)	4% (0%, 9%)	2% (-1%, 6%)
	Day 14	TRADENAME (n/N) (1)	552/851 (65%)	734/851 (86%)
		NEVANAC (n/N) (1)	568/845 (67%)	737/845 (87%)
		Difference (95% CI) (2)	2% (-2%, 7%)	1% (-2%, 4%)
Study 2	Day 7	TRADENAME (n/N) (1)	174/540 (32%)	453/540 (84%)
		Nepafenac 0.1% Once Daily (n/N) (1)	172/534 (32%)	425/534 (80%)
		Difference (95% CI) (2)	0% (-6%, 6%)	-4% (-9%, 1%)
	Day 14	TRADENAME (n/N) (1)	331/540 (61%)	456/540 (84%)
		Nepafenac 0.1% Once Daily (n/N) (1)	322/534 (60%)	439/534 (82%)
		Difference (95% CI) (2)	-1% (-7%, 5%)	-2% (-7%, 2%)

(1) n/N is the ratio of those with no treatment failure prior to Day 14 post-surgery visit and complete resolution by Day 14 post-surgery visit over all randomized subjects prior to cataract surgery.

(2) Difference is (active control – test drug). The 95% confidence interval is derived using asymptotic approximation.

APPENDIX A: Efficacy in Subgroups

Table 19: Inflammation Resolution and Pain Resolution by Age Subgroup, Treatment and Study

Studies	Treatments	Age Categories	Total *	Inflammation Resolution	Pain Resolution
			N	n (n/N)	n (n/N)
C09055	Nepafenac 0.3%	< 65	240	158 (66%)	209 (87%)
		≥ 65	607	394 (65%)	525 (86%)
	Vehicle of Nepafenac 0.3%	< 65	55	16 (29%)	26 (47%)
		≥ 65	155	51 (33%)	72 (46%)
	Nepafenac 0.1% TID	< 65	225	141 (63%)	197 (88%)
		≥ 65	618	427 (69%)	540 (87%)
	Vehicle of Nepafenac 0.1% TID	< 65	56	26 (46%)	32 (57%)
		≥ 65	157	47 (30%)	83 (53%)
C11003	Nepafenac 0.1% QD	< 65	128	69 (54%)	102 (80%)
		≥ 65	406	253 (62%)	337 (83%)
	Nepafenac 0.3%	< 65	136	71 (52%)	110 (81%)
		≥ 65	404	260 (64%)	346 (86%)
	Vehicle of Nepafenac 0.3%	< 65	74	17 (23%)	25 (34%)
		≥ 65	194	46 (24%)	76 (39%)

***** Total Randomized in each subgroup

Table 20: Resolution of Inflammation and Pain in Different Age Subgroups, Treatments and Studies

Studies	Treatments	Age Categories	Total *	Inflammation Resolution	Pain Resolution
			N	n (n/N)	n (n/N)
C09055	Nepafenac 0.3%	< 64	218	143 (66%)	190 (87%)
		64-69	192	119 (62%)	167 (87%)
		70-75	233	152 (65%)	205 (88%)
		> 75	204	138 (68%)	172 (84%)
	Vehicle of Nepafenac 0.3%	< 64	53	16 (30%)	25 (47%)
		64-69	38	12 (32%)	21 (55%)
		70-75	62	19 (31%)	26 (42%)
		> 75	57	20 (35%)	26 (46%)
	Nepafenac 0.1% TID	< 64	204	126 (62%)	177 (87%)
		64-69	227	161 (71%)	207 (91%)
		70-75	197	128 (65%)	172 (87%)
		> 75	215	153 (71%)	181 (84%)
	Vehicle of Nepafenac 0.1% TID	< 64	54	24 (44%)	30 (56%)
		64-69	54	15 (28%)	33 (61%)
		70-75	53	17 (32%)	29 (55%)
		> 75	52	17 (33%)	23 (44%)
C11003	Nepafenac 0.1% QD	< 64	107	58 (54%)	87 (81%)
		64-69	134	77 (57%)	103 (77%)
		70-75	164	98 (60%)	139 (85%)
		> 75	129	89 (69%)	110 (85%)
	Nepafenac 0.3%	< 64	120	63 (52%)	98 (82%)

		64-69	138	89 (64%)	120 (87%)
		70-75	140	87 (62%)	113 (81%)
		> 75	142	92 (65%)	125 (88%)
	Vehicle of Nepafenac 0.3%	< 64	65	17 (26%)	24 (37%)
		64-69	54	11 (20%)	21 (39%)
		70-75	83	16 (19%)	25 (30%)
		> 75	66	19 (29%)	31 (47%)

***** Total Randomized in each subgroup

Table 21: Resolution of Inflammation and Pain by Race, Treatments and Studies

Studies	Treatments	Race	Total *	Inflammation Resolution	Pain Resolution
			N	n (n/N)	n (n/N)
C09055	Nepafenac 0.3%	White	739	492 (67%)	646 (87%)
		Black	62	35 (56%)	54 (87%)
		Asian	42	22 (52%)	31 (74%)
		Other	4	3 (75%)	3 (75%)
	Vehicle of Nepafenac 0.3%	White	181	60 (33%)	87 (48%)
		Black	19	6 (32%)	9 (47%)
		Asian	10	1 (10%)	2 (20%)
		Other	0	0	0
	Nepafenac 0.1% TID	White	726	501 (69%)	637 (88%)
		Black	63	35 (56%)	54 (86%)
		Asian	50	29 (58%)	43 (86%)
		Other	4	3 (75%)	3 (75%)
	Vehicle of Nepafenac 0.1% TID	White	183	64 (35%)	96 (52%)
		Black	17	7 (41%)	11 (65%)
		Asian	12	2 (17%)	8 (67%)
		Other	1	0 (0%)	0 (0%)

C11003	Nepafenac 0.1% QD	White	451	274 (61%)	379 (84%)
		Black	40	22 (55%)	32 (80%)
		Asian	38	23 (61%)	25 (66%)
		Other	5	3 (60%)	3 (60%)
	Nepafenac 0.3%	White	469	300 (64%)	410 (87%)
		Black	40	22 (55%)	37 (92%)
		Asian	31	9 (29%)	9 (29%)
		Other	0	0	0
	Vehicle of Nepafenac 0.3%	White	231	56 (24%)	89 (39%)
		Black	19	4 (21%)	6 (32%)
		Asian	17	3 (18%)	6 (35%)
		Other	1	0 (0%)	0 (0%)

***** Total Randomized in each subgroup

Table 22: Resolution of Inflammation and Pain by Sex, Treatments and Studies

Studies	Treatments	Sex	Total *	Inflammation Resolution	Pain Resolution
			N	n (n/N)	n (n/N)
C09055	Nepafenac 0.3%	Male	357	232 (65%)	309 (87%)
		Female	490	320 (65%)	425 (87%)
	Vehicle of Nepafenac 0.3%	Male	84	31 (37%)	46 (55%)
		Female	126	36 (29%)	52 (41%)
	Nepafenac 0.1% TID	Male	369	248 (67%)	328 (89%)
		Female	474	320 (68%)	409 (86%)
	Vehicle of Nepafenac 0.1% TID	Male	94	34 (36%)	55 (59%)
		Female	119	39 (33%)	60 (50%)
C1100	Nepafenac 0.1% QD	Male	208	132 (63%)	173

					(83%)
		Female	326	190 (58%)	266 (82%)
3	Nepafenac 0.3%	Male	242	153 (63%)	204 (84%)
		Female	298	178 (60%)	252 (85%)
	Vehicle of Nepafenac 0.3%	Male	115	31 (27%)	46 (40%)
		Female	153	32 (21%)	55 (36%)

***** Total Randomized in each subgroup

Table 23: Resolution of Inflammation and Pain by Region and Treatments in Study 09055

Study	Treatments	Region	Total *	Inflammation Resolution	Pain Resolution
			N	n (n/N)	n (n/N)
C09055	Nepafenac 0.3%	EU	109	67 (61%)	88 (81%)
		US	742	485 (65%)	646 (87%)
	Vehicle of Nepafenac 0.3%	EU	27	10 (37%)	15 (56%)
		US	184	57 (31%)	83 (45%)
	Nepafenac 0.1% TID	EU	105	73 (70%)	92 (88%)
		US	740	495 (67%)	645 (87%)
	Vehicle of Nepafenac 0.1% TID	EU	27	15 (56%)	19 (70%)
		US	186	58 (31%)	96 (52%)

***** Total Randomized in each subgroup

APPENDIX B: Applicant's Efficacy Results

Table 24: Applicant's Table 2-2 in C09055 Study Report
Percent Patients Cured at Day 14
All Treatments Comparison
(Intent-to-Treat)

Nepafenac 0.3%		NEVANAC		Nepafenac Vehicle 0.3%		NEVANAC Vehicle			
N	n (%)	N	n (%)	N	n (%)	N	n (%)	p-value[a]	p-value[b]
807	552 (68.4)	811	568 (70.0)	197	67 (34.0)	205	73 (35.6)	< 0.0001	< 0.0001

Cure was defined as a patient having a score of 0 for both cells and flare at Day 14 (LOCF).
N is the number of patients with non-missing postoperative data.
n is the number of patients cured.
% is calculated as (n/N)*100.
p-value is based upon Cochran-Mantel-Haenszel controlling for site.
[a]Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
[b]NEVANAC versus NEVANAC Vehicle

Table 25: Applicant's Table 2.3 in Study C09055 Report
Percent Pain-Free Patients at Day 14
All Treatments Comparison
(Intent-to-Treat)

Nepafenac 0.3%		NEVANAC		Nepafenac Vehicle 0.3%		NEVANAC Vehicle			
N	n (%)	N	n (%)	N	n (%)	N	n (%)	p-value[a]	p-value[b]
807	734 (91.0)	811	737 (90.9)	197	98 (49.7)	205	115 (56.1)	< 0.0001	< 0.0001

Pain-free was defined as a score of 0 on the Investigator's assessment of ocular pain at Day 14 (LOCF).
N is the number of patients with non-missing postoperative data.
n is the number of patients cured.
% is calculated as (n/N)*100.
p-value is based upon Cochran-Mantel-Haenszel controlling for site.
[a]Nepafenac 0.3% versus Nepafenac Vehicle 0.3%
[b]NEVANAC versus NEVANAC Vehicle

Table 26: Applicant's Table 11.4.1.1.1.-1 in C11003 Study Report
Percent Cures at Day 14
(Intent-to-Treat)

Nepafenac 0.3%		Nepafenac Vehicle 0.3%		Nepafenac 0.3% vs
N	n (%)	N	n (%)	Nepafenac Vehicle 0.3%[a]
512	331 (64.6)	252	63 (25.0)	<0.0001

Cure was defined as a patient having a score of 0 for both cells and flare at the visit (LOCF).
N is the number of patients with non-missing post surgery data.
n is the number of patients cured.
% is calculated as (n/N)*100.
[a]p-value is from Cochran-Mantel-Haenszel test stratified by site.

Table 27: Applicant's Table 14.2.-26 in C11003 Study Report

Number and Percentage of Patients that are Pain Free at Day 14 (Intent-to-Treat)

Nepafenac 0.3% N=512		Nepafenac 0.1% N=493		Nepafenac Vehicle 0.3% N=252		Total N=1257	
N	n (%)	N	n (%)	N	n (%)	N	n (%)
512	456 (89.1)	493	439 (89.0)	252	101 (40.1)	1257	996 (79.2)

Pain free occurred when the Investigator's assessment of ocular pain was 0 at the visit.
N is the number of patients with non-missing post surgery data.
n is the number of patients with associated with the status.
% is calculated as (n/N)*100

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

/s/

RIMA IZEM
09/12/2012

YAN WANG
09/12/2012
I concur.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203491 **Applicant:** (b) (4) **Stamp Date:** 12/16/2011

Drug Name: Nepafenac 0.3% Ophthalmic Suspension **NDA Type:** Standard review

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

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

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

The following information request should be sent to applicant:

Although the dataset submission is fileable, there were several deficiencies which may result in increasing the time necessary for review. We first list the usual recommendation for submissions, for future reference. We then list the list of the deficiencies in your current submission as compared to our usual recommendations, for the record. We finally give a specific list of requests. Please provide us with a timeline to complete these requests so that we can plan for our review accordingly.

1 Usual recommendations

We usually recommend the following for dataset submission and formatting:

- *You are encouraged to submit standardized datasets following the CDISC guidelines for SDTM and ADaM datasets.*
- *Provide all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report.* ***In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.***

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

- *Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses**. In addition, provide a document that explains what each program is used for.***

- ***Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the specific analyses results contained in the ISE reports.***

- ***Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the inferential analyses results in the ISS reports.***

- *You can check the FDA website to find the information about current document and guidance.*

Link to Study Data Specifications
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf

2 List of deficiencies

Your submission did not follow our usual recommendations in the following ways

a) You submitted the efficacy data separately for each study and did not integrate the study (with same naming of variables) in an integrated summary of efficacy folder.
b) You did not distinguish between the tabulation datasets (containing all that is collected from the CRF) and analyses datasets (containing data used in main efficacy and safety analyses, with some CRF data and some derived variables).
c) The define.pdf documentation file does not specify how all the derived variables were derived.
d) You did not provide a reviewer's guide explaining which dataset and which code was used in the main primary and secondary analyses.
e) You did not follow CDISC standards for naming the variables.

3 List of Requests

1- Please provide a reviewer's guide for each trial explaining which datasets and which SAS code were used for the main analyses for primary and secondary endpoints.

2- Please provide the following datasets: note that each dataset should have a subject id, study id, study center id, treatment assignment (drug and frequency of dose):

a) An integrated demographic dataset with demographic and geographic information on all subjects from both trials. Dataset should include variables of study eye, age,

sex, race, iris color, country and center. This dataset should include these variables as used in the main efficacy and subgroup analyses.

b) An integrated subject disposition dataset. This dataset should include variable indicator whether subject is in intent to treat analysis, indicator whether subject is in the per protocol analysis, indicator whether subject completed the study, indicator of whether subject discontinued from the study, date of surgery, date of last visit, date of first taking drug, discontinuation date, reason for discontinuation, and protocol violation and reason for protocol violation.

c) An integrated efficacy dataset. For each subject and visit, visit number, visit date, study day (counting surgery date as day 1), flare score (observed, imputed and imputation flag), aqueous cell score (observed, imputed and imputation flag), pain score (observed, imputed and imputation flag).

Provide documentation for the datasets (a define.pdf document). For all variables directly copied from CRF, provide CRF page number and/or link to annotated CRF. For all derived variables, specify (in English) how the variables were derived from CRF data.

- end of information request

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		LOCF of flare and cell score was used except for those who were treatment failures (cell score > 2, flare score =3 and/or ocular pain score > 3

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief summary of controlled clinical trials
The following table is summary of pivotal trials supporting the indication. The two studies have identical design and similar results

Study number	Design	Treatment arms Total sample size	Primary endpoint/Analysis	Sponsor's findings
C-09-055	Randomized, double-masked placebo controlled, parallel arms (14 days post-cataract surgery)	(1) Nepafenac 0.3% (QD) (2) Vehicle of 0.3% dose (QD) (3)Nepafenac 0.1% (TID) (4) Vehicle of 0.1% dose (TID) Total Sample size: (2042)	Primary endpoint (1) proportion of subjects with clinical cure (cell score and flare score =0) at Day 14 , and Secondary endpoint: (2) proportion of subjects with (Grade 0) pain at day 14	(1) Nepafenac 0.3% (68%), Vehicle of 0.3% dose (34%) (p-value*< 0.0001). Nepafenac 0.1% (70%), vehicle of 0.1% dose (36%) (p-value< 0.0001) (2) Nepafenac 0.3% (91%), Vehicle of 0.3% dose (50%) (p-value*<0.0001) Nepafenac 0.1% (91%) and Vehicle of 0.1% dose (56%) (p-value* < 0.0001)
C-11-003	Randomized, double-masked placebo controlled, parallel arms (14 days post-cataract surgery)	(1) Nepafenac 0.3% (QD) (2) Nepafenac 0.1% (QD) (3) Vehicle (QD) Total Sample Size: (1282)	Primary endpoint (1) proportion of subjects with clinical cure (cell score and flare score =0) at Day 14 Secondary endpoints: (2) proportion of subjects with clinical success (cell score < 2 and flare = 0) (3) (Grade 0) pain at day 14 (4) Clinical failure (cell score > 2 and flare score =3 and/or ocular pain > 3)	(1) Nepafenac 0.3% (65%) vs Vehicle (25%), (p-value * < 0.001) Nepafenac 0.1% (65%) (2) not used in the primary analysis (3) Nepafenac 0.3% (89%), Nepafenac 0.1% (89%), Vehicle (40%) (4) not used in primary analysis

***p-value from Cochran-Mantel-Haenszel test stratified by site**

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Background:

The current drug is an NSAID (Non-steroidal anti-inflammatory drug). The proposed drug, Nepafenac 0.3% (QD), is a higher dose and lower frequency administration of an approved drug for this indication NEVANAC® (Nepafenac 0.1% TID approved in 2005, NDA 21862).

The two trials supporting the indication have different treatment arms although both trials compare the new proposed drug to its vehicle. Both trials show superiority of the new drug to its vehicle for inflammation and pain at day 14. In addition, Trial C-0955 shows non-inferiority of the proposed drug to the approved drug with a 10% margin. Trial C-11-03 show similar results of Nepafenac 0.3% (QD) to Nepafenac 0.1%(QD) for efficacy at day 14.

Rima Izem	01-26-2012
Reviewing Statistician	Date
Yan Wang	01-26-2012
Supervisor/Team Leader	Date

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

/s/

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01/30/2012

YAN WANG
01/30/2012