ARTICLE

Once-daily nepafenac ophthalmic suspension 0.3% to prevent and treat ocular inflammation and pain after cataract surgery: Phase 3 study

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PURPOSE: To evaluate once-daily nepafenac 0.3% to prevent and treat ocular pain and inflammation after cataract surgery.

SETTING: Sixty-five centers in the United States and Europe.

DESIGN: Randomized double-masked vehicle- and active-controlled phase 3 study.

METHODS: Patients received nepafenac 0.3% once daily, nepafenac 0.1% 3 times daily, or their respective vehicles from day −1 to day 14 after cataract extraction. An additional drop of study drug was administered 30 to 120 minutes preoperatively. The primary endpoint was the percentage of patients with a cure for inflammation (score of 0 for both aqueous cells and flare) at day 14.

RESULTS: Of randomized patients, 817 received nepafenac 0.3%, 819 received nepafenac 0.1%, and 200 and 206 received the respective vehicles. Significantly more nepafenac 0.3% patients had no inflammation (68.4% versus 34.0%) and were pain free (91.0% versus 49.7%) at day 14 than vehicle patients (both $P<.0001$). Nepafenac 0.3% was noninferior to nepafenac 0.1% for inflammation (95% confidence interval [CI], −5.73% to 3.17%) and pain-free rates (95% CI, −3.08% to 2.70%). At all postoperative visits, fewer treatment failures ($P\leq.0012$) and more clinical successes ($P\leq.0264$) were observed with nepafenac 0.3% versus vehicle. Nepafenac 0.3% was well tolerated and had a safety profile comparable to that of nepafenac 0.1%.

CONCLUSIONS: Once-daily nepafenac 0.3% was noninferior to nepafenac 0.1% 3 times daily for prevention and treatment of ocular inflammation and pain following cataract surgery. The safety of nepafenac 0.3% was comparable to that of nepafenac 0.1%, with the added convenience of once-daily dosing.

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Cataract is the leading cause of blindness worldwide and the main cause of reversible decreased vision in the elderly in the developed world.[1,2] Patients with cataracts have a gradual loss in visual acuity that may be accompanied by reduced physical ability and loss of self-esteem, creating a considerable social and economic burden.[3,4] In developed countries, cataract surgery is one of the most common surgical procedures performed. Overall, its high success rates yield improved visual acuity and improved patient quality of life.[1,5,6] Wider ranging positive effects include a reduced risk for hip fractures in patients who have had cataract surgery compared with matched cataract patients who have not had surgery.[7] As the mean and median age of the world population increases, the prevalence of cataracts and the number of patients in need of cataract surgery will steadily increase worldwide.[1]

Intraocular inflammation is a common event after cataract surgery. It is often managed with corticosteroid and topical antiinflammatory agents to reduce symptoms, increase comfort, and prevent complications.[8,9] The inflammatory process is mediated by the

action of cyclooxygenase (COX) enzymes that lead to the subsequent production of proinflammatory prostaglandins.[8,10] Prostaglandins have in turn been linked to disruption of the blood–aqueous barrier and increases in vascular permeability changes associated with inflammation and edema.[11,12] Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of COX enzymes and prostaglandin production. The efficacy and safety of topical NSAIDs in treating postsurgical ocular inflammation and pain are well established, and the relative merits and risks of NSAIDs versus postoperative topical steroids have been addressed by several authors.[8,10]

Nepafenac ophthalmic suspension 0.1% (nepafenac 0.1%) (Nevanac) is a topical ocular NSAID used to prevent and treat the pain and inflammation associated with cataract surgery.[13,A] In contrast to other ocular NSAIDs, nepafenac is a prodrug that rapidly penetrates the cornea and is deaminated by intraocular hydrolases within ocular tissues to form the active metabolite amfenac.[13,A] Nepafenac and amfenac are potent inhibitors of the COX enzymes COX-1 and COX-2.[14,15] The bioconversion of nepafenac is greatest in vascularized tissues, such as the iris and ciliary body and, to a greater extent, the retina and choroid,[15] the region of the eye with the greatest prostaglandin concentrations and COX activity.[16]

Clinical studies[13,17–19] have shown that nepafenac 0.1% taken 3 times daily beginning the day before surgery is well tolerated and effective in the treatment of the ocular inflammation and pain associated with cataract surgery. Furthermore, recent studies[20,21] have found that nepafenac 0.1% is effective in reducing macular edema secondary to cataract extraction and macular edema associated with diabetes. Nepafenac 0.1% is approved by the European Medicines Agency but not by the United States Food and Drug Administration to reduce the risk for macular edema that can occur after cataract surgery in patients with diabetes.[B]

A new formulation of nepafenac ophthalmic suspension (nepafenac 0.3%) that can be used once a day to prevent and treat ocular inflammation and pain after cataract surgery has been developed and recently approved for use in the U.S.[C] In addition to its higher concentration of the active molecule, nepafenac 0.3% has a reduced particle size compared with nepafenac 0.1%, which increases the surface area for dissolution, and added guar, a retention agent that enhances the bioavailability of nepafenac in the eye over that with nepafenac 0.1%. Here, we report the results of a phase 3 study that evaluated the safety and efficacy of nepafenac 0.3% taken once daily relative to nepafenac 0.1% 3 times daily and the respective vehicles for the prevention and treatment of ocular inflammation and pain 14 days after cataract extraction.

PATIENTS AND METHODS

Study Design

This randomized double-masked parallel-group multicenter vehicle- and active-controlled phase 3 study was performed at 65 centers in Europe (Hungary, Italy, Sweden, and Switzerland) and the United States between June 2010 and May 2011. Eligible patients were randomized (4:4:1:1) to receive nepafenac 0.3% once daily, nepafenac 0.1% 3 times daily, or their respective vehicles.

The study consisted of 6 visits as follows: a screening/baseline visit (performed within 2 days to 6 weeks before the surgery visit), the cataract surgery visit (day 0), and 4 postoperative visits (days 1, 3, 7, and 14). Patients began instilling the study drug—dosed once daily if assigned to nepafenac 0.3% or its vehicle or 3 times daily if assigned to nepafenac 0.1% or its vehicle—into the study eye on the day before cataract surgery (day −1). Dosing continued on the day of surgery (day 0) and for 14 days thereafter. On the day of surgery, designated study personnel instilled 1 additional drop of the assigned study drug into each patient's study eye 30 to 120 minutes before surgery. All patients received the investigator's standard regimen of preoperative, intraoperative, and postoperative care with the exception of NSAID and steroid use. During the study, all patients, investigators, and study-related personnel were masked to the treatment assignment, and all personnel involved in efficacy assessments and analysis of results were masked to the dosing frequency.

The study was performed in accordance with Good Clinical Practices and the ethical principles described in the Declaration of Helsinki. An institutional review board/independent ethics committee in each associated country approved the protocol. On entry, all participating patients provided written informed consent. This study is registered at clinicaltrials.gov as NCT01109173.[D]

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Patients

Male and female patients aged 18 years or older who had a planned cataract extraction by phacoemulsification with the implantation of a posterior chamber intraocular lens (IOL) were eligible for inclusion. Patients who had a history of ocular surgery, inflammatory eye disease, ocular infection, congenital ocular anomalies, uncontrolled glaucoma, diabetic retinopathy, and ocular trauma or current signs and symptoms that were associated with these or other ocular conditions were excluded. Additional exclusion criteria were planned multiple procedures for the study eye during cataract extraction and IOL implantation, use of steroids by any route within 14 days of surgery, and use of NSAIDs by any route within 7 days of surgery (except an allowed daily dose of 100 mg aspirin). Use of steroids and other topical ocular or systemic NSAIDs was also prohibited for the duration of the study.

Endpoints and Assessments

Efficacy All patients were evaluated for efficacy and safety on days 1, 3, 7, and 14 or at the time of earlier discontinuation from the study. The primary efficacy endpoint was the percentage of patients at day 14 whose inflammation had resolved (considered cured), defined as a score of 0 for aqueous cells and flare. Ocular inflammation (cells and flare) was assessed by the investigators at the screening/baseline visit and at all postoperative visits using slitlamp biomicroscopy. Inflammatory cells were graded using a scale that ranged from 0 (none) to 4 (more than 30 cells). Flare was graded using a scale that ranged from 0 (no visible flare compared with the normal eye) to 3 (severe; very dense flare).

The secondary efficacy endpoint was the percentage of patients who were pain free at day 14, defined as an ocular pain assessment score of 0. Ocular pain was assessed by patient reports to the investigators at the screening/baseline visit and at all postoperative visits. Ocular pain was documented using a categorical scale that ranged from 0 (none) to 5 (severe).

In addition to the primary and secondary endpoints, a series of prespecified supportive efficacy endpoints were included as follows: the percentage of cumulative cures by visit (resolution of inflammation by visit) (ie, the percentage of patients who met the definition of a cure at each visit and remained cured at all subsequent visits), the cumulative pain-free rates by visit (ie, the percentage of patients who met the definition of pain free at each visit and remained pain free at all subsequent visits), and the percentage of patients who were declared treatment failures at each visit. A patient was classified as a treatment failure if he or she had an aqueous cells score of 3 or higher, an aqueous flare score of 3, and/or an ocular pain score of 4 or higher.

The percentage of patients in each treatment group who achieved clinical success was evaluated as a planned exploratory analysis of the primary variable. For this analysis, clinical success was defined as a cells score of 1 or less (0 to 5 cells) and a flare score of 0.

Safety Information on adverse events was collected for all patients after the first administration of study drug on day −1 and continued through day 14 (or early exit). All reported and observed adverse events were assessed according to their seriousness, severity (mild, moderate, or severe), relationship to the study drug, individual characteristics (eg, onset, duration, and outcome), and whether they resulted in patient discontinuation from the study.

In addition to a review of reported adverse events, the safety of nepafenac 0.3% was assessed by routine ocular examinations. Specifically, the safety review included intraocular pressure (IOP) measurements, other ocular outcomes (chemosis, bulbar conjunctival injection, corneal edema) derived from slitlamp biomicroscopy evaluations, dilated fundus parameters (retina/macula/choroid, optic nerve), and results of corrected distance visual acuity (CDVA) assessments.

Statistical Analysis

Efficacy analyses were performed with the intent-to-treat analysis set, which included all randomized patients who received the study drug and had at least 1 on-therapy postsurgical visit. Safety was evaluated for all patients who received exposure to the study drug or potential exposure to the study drug (ie, patients who discontinued the study before surgery but returned an opened bottle of study drug or failed to return the study drug).

A sample size of 800 patients in each of the nepafenac groups and 200 patients in each of the corresponding vehicle groups was calculated to provide a statistical power of 98% to show nepafenac 0.3% instilled once daily was noninferior to nepafenac 0.1% instilled 3 times daily and a statistical power of 99% to show superiority of nepafenac 0.3% and nepafenac 0.1% compared with their respective vehicles in terms of the proportion of patients who achieve a clinical cure. The cure rate in the nepafenac groups and vehicle groups was assumed to be 70% and 50%, respectively. Testing to determine whether nepafenac 0.3% was as effective as nepafenac 0.1% used the 2-sided 95% confidence interval (CI) approach derived from the method of Yanagawa et al.[22] The noninferiority margin was 10%; thus, to show that nepafenac 0.3% was as effective as nepafenac 0.1%, the lower limit of the 2-sided 95% CI had to be greater than −10%. Pairwise superiority testing for comparisons of each active treatment to their respective vehicles was performed using the 2-sided Cochran-Mantel-Haenszel test controlling for investigational center with a significance level of 0.05. Supportive endpoints were described using summary statistics by treatment group and visit.

To ensure the type 1 error rate was controlled at the 5% level, a gate-keeping multiplicity strategy was used. All 3 co-primary hypotheses must be rejected for a successful study, and conclusion from the 3 secondary endpoint hypotheses was only possible after rejection of the primary endpoint hypotheses. In addition, successful conclusion of the investigator assessment of ocular pain was possible only if all 3 hypotheses were rejected and the primary endpoint was met. Multiplicity adjustment was not applied on the supportive endpoints. All statistical analyses were performed using SAS software (version 9.2, SAS Institute, Inc.).

RESULTS

Patient Characteristics and Disposition

Of the 2120 patients enrolled in the study, 78 were excluded from the safety populations (n = 2042) because they did not receive study medication. A further 20 patients were dispensed study medication but discontinued on the day of surgery and had no on-therapy follow-up efficacy data collected. The intent-to-treat population comprised 2022 patients who received study medication and had at least 1 on-therapy

postsurgical visit. The most common reason for study discontinuation was treatment failure (190 patients [9.0%]) followed by non-use of study medication (78 patients [3.7%]) and adverse events (47 patients [2.2%]). Discontinuation due to treatment failure was similar between the 2 nepafenac treatment groups (n = 25 [2.9%] and n = 32 [3.8%] for nepafenac 0.3% and 0.1%, respectively) and between the 2 vehicle groups (n = 69 [32.7%] and n = 64 [30.0%], respectively).

The distribution of demographic and baseline characteristics were well balanced, with no clinically relevant differences between groups (Table 1). The majority of patients were 65 years of age or older, women, and white.

Efficacy

Ocular Inflammation Table 2 shows an analysis of ocular inflammation and the absence of ocular pain at 14 days in the intent-to-treat population. The lower boundary of the 95% CI calculated from the difference in the percentage of patients achieving cure at day 14 was −5.73%. Thus, based on a prespecified margin of −10%, nepafenac 0.3% instilled once daily was noninferior to nepafenac 0.1% instilled 3 times daily for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

Significantly more patients in the nepafenac 0.3% and nepafenac 0.1% groups than patients in the respective vehicle groups achieved a cure at day 14 (both $P<.0001$) (Table 2). Thus, both nepafenac groups were superior to their respective vehicles for the prevention and treatment of ocular inflammation 14 days after cataract extraction.

From day 7, the observed cumulative percentage of patients who were cured in the nepafenac 0.3% group was higher than in the nepafenac 0.3% vehicle group ($P<.0001$ for pairwise comparisons at day 7 and day 14) (Figure 1). The percentage of patients cured was also higher in the nepafenac 0.1% group than in the nepafenac 0.1% vehicle group beginning at postoperative day 3 ($P<.0001$ for pairwise comparisons at days 3, 7, and 14).

Ocular Pain The lower boundary of the 95% CI calculated from the difference in the percentage of patients in each group who were pain free was −3.08% (Table 2), showing that nepafenac 0.3% once daily was noninferior to nepafenac 0.1% 3 times daily for the prevention and treatment of ocular pain 14 days after cataract extraction.

Significantly more patients in the nepafenac 0.3% and nepafenac 0.1% groups were pain free at day 14 than patients in the respective vehicle groups (both $P<.0001$) (Table 2). Thus, each active treatment was

Table 1. Demographic and baseline characteristics, intent-to-treat population.

Parameter	Nepafenac 0.3% (n = 807)	Nepafenac 0.1% (n = 813)	Nepafenac 0.3% Vehicle (n = 197)	Nepafenac 0.1% Vehicle (n = 205)	Total (n = 2022)
Age (y)					
Mean ± SD	68.7 ± 9.08	68.8 ± 9.31	69.8 ± 9.31	68.9 ± 9.37	68.9 ± 9.22
Range	32, 89	20, 90	38, 92	38, 90	20, 92
Age Category, n (%)					
<65 years	233 (28.9)	220 (27.1)	51 (25.9)	55 (26.8)	559 (27.6)
≥65 years	574 (71.1)	593 (72.9)	146 (74.1)	150 (73.2)	1463 (72.4)
Sex, n (%)					
Male	342 (42.4)	355 (43.7)	79 (40.1)	90 (43.9)	866 (42.8)
Female	465 (57.6)	458 (56.3)	118 (59.9)	115 (56.1)	1156 (57.2)
Race, n (%)					
White	708 (87.7)	702 (86.3)	170 (86.3)	175 (85.4)	1755 (86.8)
Black or African American	59 (7.3)	59 (7.3)	17 (8.6)	17 (8.3)	152 (7.5)
Asian	36 (4.5)	48 (5.9)	10 (5.1)	12 (5.9)	106 (5.2)
American Indian/Alaska Native	1 (0.1)	0	0	0	1 (0.0)
Multiracial	1 (0.1)	2 (0.2)	0	1 (0.5)	4 (0.2)
Other	2 (0.2)	2 (0.2)	0	0	4 (0.2)
Iris color, n (%)					
Brown	379 (47.0)	373 (45.9)	83 (42.1)	93 (45.4)	928 (45.9)
Hazel	105 (13.0)	97 (11.9)	26 (13.2)	23 (11.2)	251 (12.4)
Green	67 (8.3)	61 (7.5)	15 (7.6)	13 (6.3)	156 (7.7)
Blue	236 (29.2)	267 (32.8)	70 (35.5)	73 (35.6)	646 (31.9)
Gray	14 (1.7)	12 (1.5)	1 (0.5)	2 (1.0)	29 (1.4)
Other	6 (0.7)	3 (0.4)	2 (1.0)	1 (0.5)	12 (0.6)

Table 2. Analysis of ocular inflammation and absence of ocular pain at day 14 in the intent-to-treat population.

Parameter	Nepafenac 0.3% (N = 807)	Nepafenac 0.1% (N = 811)*	Nepafenac 0.3% Vehicle (N = 197)	Nepafenac 0.1% Vehicle (N = 205)
Ocular inflammation				
Cured, n (%)	552 (68.4)	568 (70.0)	67 (34.0)	73 (35.6)
95% CI†	−5.73, 3.17		—	—
P value	—	—	<.0001‡	<.0001§
Ocular pain				
Pain free, n (%)	734 (91.0)	737 (90.9)	98 (49.7)	115 (56.1)
95% CI†	−3.08, 2.70		-	-
P value	—	—	<.0001‡	<.0001§

CI = confidence interval; Cured = inflammation resolved
*Two patients were randomized but did not have on-study data
†Test-based CI for the difference in treatment percentages (nepafenac 0.3% minus nepafenac 0.1%)
‡Nepafenac 0.3% versus nepafenac 0.3% vehicle
§Nepafenac 0.1% versus nepafenac 0.1% vehicle

superior to its respective vehicle for the prevention and treatment of ocular pain 14 days after cataract extraction.

The cumulative percentage of patients who were pain free in the nepafenac 0.3% and nepafenac 0.1% groups was higher than in their respective vehicle groups at all postoperative visits from day 1 through day 14 ($P<.0001$ for all pairwise comparisons at each study visit) (Figure 2).

Clinical Success Rates

The cumulative clinical success rate at day 14 was 85.6% in the nepafenac 0.3% once daily (n = 691) and nepafenac 0.1% 3 times daily (n = 694) groups; the rates were 43.1% (n = 85) and 47.8% (n = 98) in the respective vehicle groups. The cumulative percentage of patients who were clinical successes was greater in the nepafenac 0.3% group than in the nepafenac 0.3% vehicle group at all postoperative visits ($P=.0264$ at day 1; $P<.0001$ at days 3, 7, and 14). The percentage of clinical successes was greater in the nepafenac 0.1% group than in the nepafenac 0.1% vehicle group on days 1, 3, 7, and 14 ($P<.0001$ at all timepoints except day 1) (Figure 3).

The cumulative percentage of patients assessed as treatment failures in the nepafenac 0.3% and nepafenac 0.1% groups was lower than in the respective

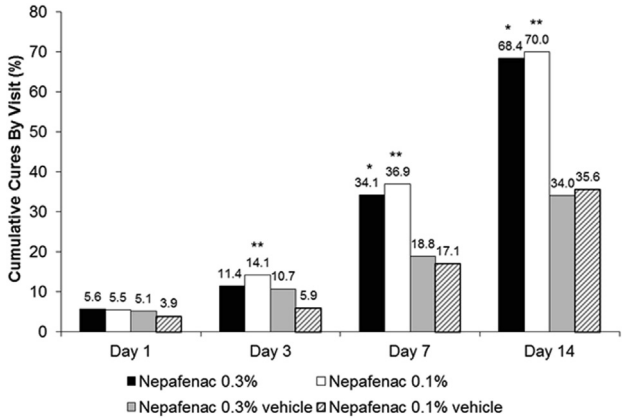

Figure 1. Percentage of cumulative cures by visit (intent-to-treat population). For once-daily nepafenac 0.3%, n = 804 at day 1 and n = 807 at all subsequent visits; for nepafenac 0.1% 3 times daily, n = 811 at all visits; for nepafenac 0.3% vehicle, n = 196 at day 1, and n = 197 at all subsequent visits; and for nepafenac 0.1% vehicle, n = 205 at all visits (* = significant difference between nepafenac 0.3% and nepafenac 0.3% vehicle [$P<.0001$]; ** = significant difference between nepafenac 0.1% and nepafenac 0.1% vehicle [$P<.0001$]).

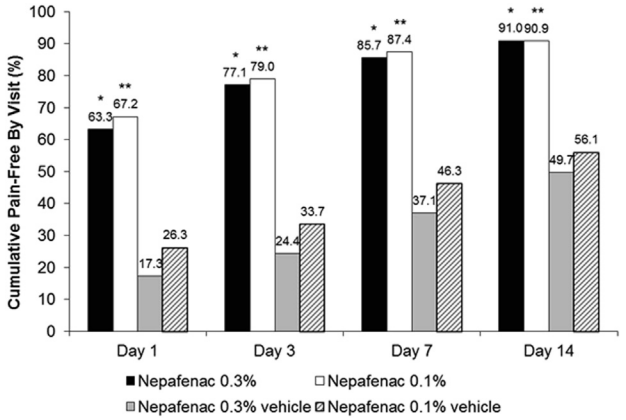

Figure 2. Cumulative percentage of patients pain free by visit (intent-to-treat population). For once-daily nepafenac 0.3%, n = 804 at day 1 and n = 807 at all subsequent visits; for nepafenac 0.1% 3 times daily, n = 811 at all visits; for nepafenac 0.3% vehicle, n = 196 at day 1 and n = 197 at all subsequent visits; and for nepafenac 0.1% vehicle, n = 205 at all visits (* = significant difference between nepafenac 0.3% and nepafenac 0.3% vehicle [$P<.0001$]; ** = significant difference between nepafenac 0.1% and nepafenac 0.1% vehicle [$P<.0001$]).

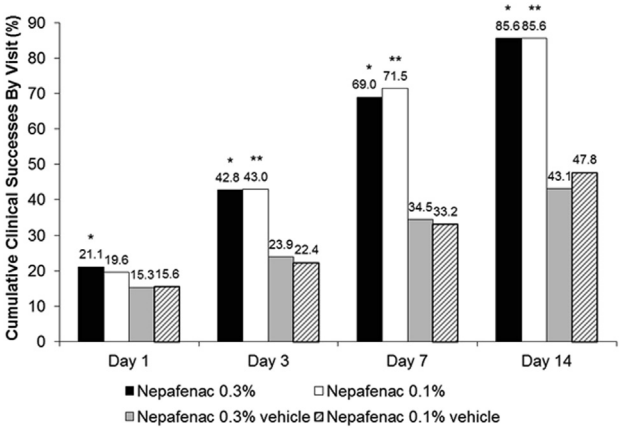

Figure 3. Cumulative percentage of patients considered clinical successes by visit (intent-to-treat population). For once-daily nepafenac 0.3%, n = 804 at day 1 and n = 807 at all subsequent visits; for nepafenac 0.1% 3 times daily, n = 811 at all visits; for nepafenac 0.3% vehicle, n = 196 at day 1 and n = 197 at all subsequent visits; and for nepafenac 0.1% vehicle, n = 205 at all visits (* = significant difference between nepafenac 0.3% and nepafenac 0.3% vehicle [$P \leq .0264$]; ** = significant difference between nepafenac 0.1% and nepafenac 0.1% vehicle [$P < .0001$]).

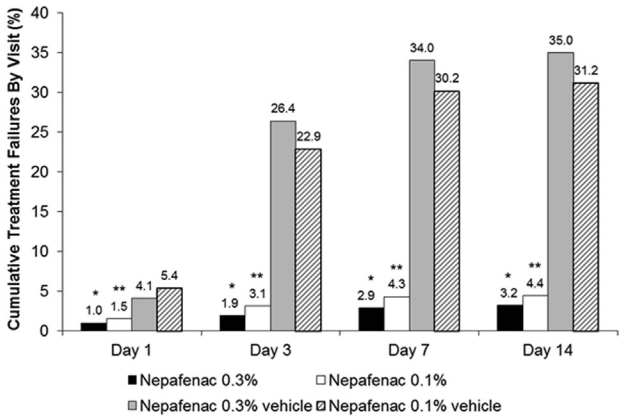

Figure 4. Treatment failures by visit (intent-to-treat population). For once-daily nepafenac 0.3%, n = 807; for nepafenac 0.1% 3 times daily, n = 811; for nepafenac 0.3% vehicle, n = 205; and for nepafenac 0.1% vehicle, n = 205 (* = significant difference between nepafenac 0.3% and nepafenac 0.3% vehicle [$P \leq .0012$]; ** = significant difference between nepafenac 0.1% and nepafenac 0.1% vehicle [$P \leq .0006$]).

vehicle groups at all postoperative visits ($P \leq .0012$ in each pairwise comparison for every study visit) (Figure 4).

Safety

Overall, once-daily nepafenac 0.3% was well tolerated by patients. Across the treatment groups, 253 patients (12.4%) reported an adverse event during the study. Of these, 3 patients were considered by the investigators to have experienced an adverse event related to treatment (Table 3). All 3 events were nonserious, were of mild to moderate intensity, and resolved with or without treatment. One patient in the nepafenac 0.3% group who reported hypersensitivity to the study drug discontinued the study. The remaining 2 events involved eye pain (1 in the nepafenac 0.3% group and 1 in the nepafenac 0.1% vehicle group).

In total, 47 patients discontinued the study due to nonserious adverse events (Table 3). With the

Table 3. Adverse event characteristics and key adverse events (safety population).

Parameter	Number (%)			
	Nepafenac 0.3% (n = 817)	Nepafenac 0.1% (n = 819)	Nepafenac 0.3% Vehicle (n = 201)	Nepafenac 0.1% Vehicle (n = 205)
Patients with at least 1 TEAE	99 (12.1)	82 (10.0)	39 (19.4)	33 (16.1)
Patients with any nonfatal SAE	7 (0.9)	3 (0.4)	0	0
Discontinuations due to AE	15 (1.8)	17 (2.1)	9 (4.5)	6 (2.9)
Discontinuations due to nonfatal SAE	2 (0.2)	2 (0.2)	0	0
Related to treatment	0	0	0	0
Discontinuations due to nonfatal SAE	13 (1.6)	15 (1.8)	9 (4.5)	6 (2.9)
Related to treatment	1 (0.1)	0	0	0
Most frequent AEs*				
Headache	22 (2.7)	13 (1.6)	3 (1.5)	3 (1.5)
IOP increase	8 (1.0)	7 (0.9)	0	0
TEAE related to treatment				
Eye pain	1 (0.1)	0	0	1 (0.5)
Hypersensitivity†	1 (0.1)	0	0	0

AE = adverse event; IOP = intraocular pressure; SAE = serious adverse event; TEAE = treatment-emergent adverse event
*Reported for ≥1% of patients in either active treatment group
†Led to patient discontinuation from study

exception of 1 patient in the nepafenac 0.3% group who reported hypersensitivity, none of the events that led to discontinuation were considered by the investigators to be treatment related. No deaths occurred during the study. Ten patients experienced serious adverse events, including 7 in the nepafenac 0.3% group and 3 in the nepafenac 0.1% group, none of which were considered by the investigators to be treatment related. Two patients each in the nepafenac 0.3% and nepafenac 0.1% groups discontinued the study due to nonfatal serious adverse events (1 report each of brain edema, injury, cerebrovascular accident, and sepsis).

The most common ocular adverse event was increased IOP, while the most common nonocular adverse event was headache (Table 3). Two patients experienced a change in IOP of 40 mm Hg or greater during the study; 1 patient receiving nepafenac 0.3% had a change of 43 mm Hg from a baseline value of 11 mm Hg, and 1 patient receiving nepafenac 0.1% had a change of 56 mm Hg from a baseline value of 12 mm Hg. All instances of increased IOP and headache were mild to moderate in intensity, resolved with or without treatment, and were considered by the investigators to be unrelated to the study drugs. With the exception of 1 patient in the nepafenac 0.3% group who discontinued due to elevated IOP, these events did not result in patient discontinuations from the study. No clinically relevant changes from baseline were observed in the CDVA, IOP, dilated fundus parameters, or ocular signs.

DISCUSSION

In this phase 3 randomized controlled study, once-daily dosing with nepafenac 0.3% was as effective as dosing 3 times daily with nepafenac 0.1% for the prevention and treatment of ocular inflammation and pain after cataract surgery. Furthermore, nepafenac 0.3% and nepafenac 0.1% were superior to their respective vehicles for all efficacy endpoints, with fewer treatment failures and more patients achieving clinical cure. By day 14, 68.4% of patients treated with once-daily nepafenac 0.3% were cured and 91.0% were pain free. The results in this study are consistent with those in previous studies of nepafenac 0.1% 3 times daily,[13,17–19] which found that nepafenac 0.1% was superior to its vehicle in terms of ocular inflammation cure rates, pain-free rates, and clinical successes in patients after cataract surgery.

The percentage of patients who achieved clinical success was higher in patients who received once-daily nepafenac 0.3% than in those who received nepafenac 0.3% vehicle ($P \leq .0264$). This difference was observed from as early as 1 day postoperatively and persisted throughout the duration of the study on days 3, 7, and 14. These findings are consistent with the mechanism of action of nepafenac and the preoperative dosing of nepafenac, which suppresses inflammation at the time of surgical trauma. The higher concentration of nepafenac 0.3% in the tissue before surgery is expected to inactivate COX enzyme activity to a greater extent, reduce the magnitude of the inflammatory response, and facilitate resolution of trauma-induced inflammation. Similar findings were observed for nepafenac 0.1% versus its control group, with significantly more patients achieving clinical success from day 3.

The clinical success endpoint is an important indicator that ocular inflammation has resolved to the point that no further treatment is necessary. This is particularly important at present because of the improvements in cataract surgery over the past decades and the related high patient expectations for rapid recovery after surgery.[9] Clinical success as measured in this study is a practical, less subjective endpoint because a single cell in the anterior chamber may be seen in patients who have not had surgery and do not have existing inflammation.[23,24] Functionally, because the clinical success endpoint allows some variability (trace, 0 to 5 cells) around the evaluation, it is more likely that the patient will be categorized correctly rather than forcing a distinction between cleared and trace, when the appearance of 1 cell in the slitlamp field may determine that difference.

The high clinical success rates with nepafenac 0.3% once daily and nepafenac 0.1% 3 times daily are supported by the corresponding low number of treatment failures. At day 14, nepafenac 0.3% once daily was associated with the lowest rate of treatment failure. Postoperatively, nepafenac 0.3% with once-daily administration is expected to be more convenient for patients, with the potential of improving dosing compliance.[25] This may be particularly important in elderly patients, for whom compliance is a concern.[26]

Postoperative inflammation remains a key cause of patient discomfort and delayed recovery after cataract surgery.[9] Nepafenac 0.3% dosed once daily was as effective as nepafenac 0.1% 3 times daily and superior to the nepafenac 0.3% vehicle for ocular inflammation endpoints at day 14. Increased IOP is a common early occurrence after cataract surgery,[27,28] and the incidences of increased IOP in the present study were similar in the nepafenac 0.3% group and nepafenac 0.1% group (1.0% and 0.9%, respectively). The majority of the reported cases of increased IOP occurred early (on day 2 or day 3) and resolved with treatment within 1 day. Furthermore, no clinically relevant changes from baseline in CDVA, dilated fundus parameters, or ocular signs were observed.

The above findings are supported by the overall safety findings in this study. Nepafenac 0.3% was

well tolerated and associated with a low incidence of treatment-related adverse events. Overall, the safety data for nepafenac 0.3% once daily and nepafenac 0.1% 3 times daily were consistent with results in previous clinical studies of nepafenac 0.1% 3 times daily.[13,17–19] Nepafenac 0.3% used once daily at a higher concentration had a safety profile similar to nepafenac 0.1% used 3 times daily in adult and elderly patients who had cataract surgery.

This was a large randomized controlled double-masked study of 2022 patients 65 years of age or older that assessed the efficacy and safety of once-daily nepafenac 0.3% for up to 14 days. The risk for cataract increases with age, and age-related cataracts are among the most common form.[1] Although pharmacologic intervention in the study was controlled, the investigators used their own standard surgical methods on all patients. Therefore, slight differences between the techniques and procedures used by cataract surgeons were not addressed in this study; nonetheless, results showed very little variability. Further studies are needed to assess the relative efficacy of nepafenac 0.3% versus other topical NSAIDs after cataract surgery.

Nepafenac 0.3% instilled once daily was as effective as nepafenac 0.1% instilled 3 times daily for the prevention and treatment of ocular inflammation and pain after cataract surgery. Nepafenac 0.3% was well tolerated, with a safety profile comparable to that of nepafenac 0.1%. The once-daily dosing regimen of nepafenac 0.3% may improve treatment outcomes after cataract surgery through increased compliance and reduced treatment burden.

WHAT WAS KNOWN

- Nepafenac 0.1% dosed 3 times daily beginning the day before surgery and for up to 14 days after cataract surgery is safe and effective for reducing postoperative ocular inflammation and pain.

WHAT THIS PAPER ADDS

- The efficacy and safety profiles of nepafenac 0.3% instilled once daily beginning the day before surgery and for up to 14 days after surgery were comparable to those of nepafenac 0.1% instilled 3 times daily for the same duration.
- Nepafenac 0.3%, a new formulation of nepafenac with once-daily dosing, decreases the treatment burden, which could improve treatment compliance and therapeutic outcomes.

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