Prospective randomised clinical trial to evaluate the safety and efficacy of nepafenac 0.1% treatment for the prevention of macular oedema associated with cataract surgery in patients with diabetic retinopathy

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ABSTRACT

Background/aims This study evaluated nepafenac ophthalmic suspension 0.1% for prevention of macular oedema (MO) when used 90 days following cataract surgery in patients with diabetic retinopathy (DR).

Methods Randomised, double-masked, vehicle-controlled, parallel group study conducted at 32 centres across the world. Participants were patients with diabetes with non-proliferative diabetic retinopathy scheduled for cataract surgery with (posterior chamber) intraocular lens implantation. Patients were randomised to nepafenac ophthalmic suspension 0.1% or vehicle three times daily, beginning on the day before surgery and continuing through the last study visit (day 90 or early exit). All patients were instilled one drop of tobramycin 0.3% and dexamethasone 0.1% four times daily for 2 weeks after surgery. Primary efficacy end point was the percentage of patients who developed MO (defined as $\geq 30\%$ increase in central subfield macular thickness from baseline) within 90 days following surgery. The secondary end point was mean change in best-corrected visual acuity (BCVA) from baseline to day 90.

Results A total of 175 patients were randomised, with 87 and 88 patients in the nepafenac and vehicle groups, respectively. A significantly greater percentage of eyes in the vehicle group (17.5%; 95% CI 9.9% to 27.6%) developed MO within 90 days following surgery compared with the nepafenac group (5.0%; 95% CI 1.4% to 12.3%, $p=0.01$). Mean change in BCVA from baseline to day 90 following surgery was greater in the nepafenac group (17.7 ± 14.6 letters) relative to the vehicle group (14.3 ± 13.9 letters), though the difference was not statistically significant ($p=0.14$). No new safety issues or trends were identified.

Conclusions A 90-day nepafenac treatment regimen prevented MO after cataract surgery in patients with DR and demonstrated no safety issues within this study group.

Trial registration number NCT00782717 and NCT00939276.

INTRODUCTION

Macular oedema (MO) is a postoperative complication of cataract surgery that typically develops 4–12 weeks after the procedure.¹ Approximately 2% of patients who undergo uncomplicated cataract surgery develop MO that is associated

with vision loss. Anatomical assessments based on optical coherence tomography (OCT) suggest that MO develops in as many as 40% of eyes, though incidence rates vary depending on the presence of predisposing factors, such as diabetic retinopathy (DR) or uveitis, and the method of detection, whether OCT, fluorescein angiography or clinical examination.^{2–4} The incidence of MO associated with cataract surgery is higher among patients with diabetes compared with those without. More than 75% of patients with mild or moderate DR have vascular leakage after cataract surgery, and more than 3% of patients with diabetes develop MO with clinically significant vision loss within 12 months of surgery, regardless of DR status.^{4–5} The threshold for developing MO may be lower in patients with diabetes due to hyperglycaemia that is associated with increased intraocular levels of advanced glycation end products, reactive oxygen species and proinflammatory factors that weaken retinal vasculature and disrupt the blood-retina barrier.⁶

Inflammation associated with cataract surgery is routinely managed with a postoperative regimen of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or a combination of both. NSAIDs reduce the activity of inflammatory pathways, including those that lead to MO, by inhibiting cyclo-oxygenase enzymes that convert cell membrane phospholipids to prostaglandin precursors.^{1–7} Clinical trials have been performed to compare the safety and efficacy of topical ophthalmic NSAIDs, including diclofenac, ketorolac, bromfenac and nepafenac, with corticosteroids or corticosteroid-NSAID combinations in the prevention of MO associated with cataract surgery.^{8–13} Overarching conclusions from these trials support a role for NSAIDs in prevention of MO associated with cataract surgery, but interpretation of the findings are limited as many of the studies did not include a vehicle control, included a small number of patients or followed postsurgical outcomes over a short duration (6 weeks or less).

Nepafenac ophthalmic suspension 0.1% (NEVANAC, Alcon Research, Fort Worth, Texas, USA) is a topical ophthalmic NSAID approved in multiple countries for the treatment of pain and inflammation associated with cataract surgery.¹⁴ Nepafenac is a prodrug that rapidly penetrates the

cornea to achieve high ocular bioavailability in the aqueous humour.¹⁵ Intraocular hydrolases in the iris, ciliary body and retina convert nepafenac to amfenac, which is a potent inhibitor of cyclo-oxygenase activity.^{15 16} Amfenac has high ocular bioavailability in the aqueous humour, and in the vitreous.^{15 17} The safety and efficacy of an extended 90-day course of nepafenac 0.1% for the prevention of MO associated with cataract surgery in patients with DR is supported by the findings of a previously reported randomised, double-masked, vehicle-controlled clinical trial.¹⁸

The primary objectives of this study were to evaluate the safety and efficacy of nepafenac 0.1% for the prevention of MO (defined as $\geq 30\%$ increase in central subfield macular thickness (CSMT) from baseline^{18 19}) when used for 90 days following cataract surgery in patients with DR.

MATERIALS AND METHODS

Study objective and methodology

This was a multicentre, randomised, double-masked, vehicle-controlled, parallel group study designed to evaluate the hypothesis that nepafenac 0.1% is safe and efficacious for the prevention of MO when used for 90 days following cataract surgery in patients with DR. Patients were evaluated on day 1, day 7, day 14, day 30, day 60 and day 90 (or at time of early discontinuation from the study (ie, early exit)). Investigators determined whether patients should be discontinued from the study based on occurrence of the following criteria: CSMT increase of 30% or more from baseline,^{18 19} best-corrected visual acuity (BCVA) decreases considered by the investigator to be associated with retinal thickening or presence of cystoid abnormalities detected by spectral domain OCT (SD-OCT).

The study was conducted in accordance with Good Clinical Practices and the ethical principles that have their origins in the Declaration of Helsinki. All participating patients provided their written informed consent. The study protocol and associated informed consent forms were reviewed and approved by institutional review boards and independent ethics committees for each investigational centre. More information on study methodology is in the online supplementary section.

Efficacy assessments

The primary outcome measure for this study was the percentage of patients who developed MO within 90 days following cataract surgery. The secondary outcome measure was mean change in BCVA from baseline to day 90. Macular thickness and macular volume were measured for the study eye using SPECTRALIS SD-OCT (Heidelberg Engineering, Carlsbad, California, USA) or Zeiss Cirrus SD-OCT (Carl Zeiss Meditec, Dublin, California, USA) at the screening visit and on day 7, day 14, day 30, day 60 and day 90 (or early exit). BCVA was assessed at each visit using the standardised Early Treatment Diabetic Retinopathy Study (ETDRS) procedure requiring certified refractionists, examiners and rooms. Study eye assessments were conducted at the baseline visit and on day 1, day 7, day 14, day 30, day 60 and day 90 (or early exit). Manifest refraction was preferred on day 1 but pinhole correction may have been performed at the discretion of the investigator with documentation.

Safety assessments

Information on adverse events (AEs) was collected for all patients after the first administration of study drug on day 1 and during all postoperative visits through day 90 (or early exit).

More information on the safety assessment is in the online supplementary section.

Study population

This study was planned to enrol approximately 222 evaluable patients (111 patients in each treatment group) to have 90% power to detect a 50% reduction in the incidence of MO (42% to 21%) within 90 days of cataract surgery for nepafenac 0.1% relative to vehicle. The sample size for this study was guided by a MO incidence rate of 42% in patients with DR.²⁰

Between August 2009 and August 2011, study investigators enrolled and treated 175 patients (first patient screened to last patient exited) at 32 investigational centres across Europe, India, Israel, New Zealand and the USA. As a result of patient recruitment difficulties, enrolment was terminated in May 2011. Patients who had been randomised and were undergoing treatment were allowed, at the discretion of the investigator, to complete the study as planned but no new patients were screened or enrolled after this point. Of the 175 patients, 9 patients did not undergo surgery and were excluded from both the safety and intent-to-treat (ITT) population and another 6 patients that did not have any postbaseline visit were excluded from the ITT population. A total of 160 patients were included in the ITT analysis population and 166 patients were included in the safety analysis population (see online supplementary figure S1). More information on the patient population is in the online supplementary section.

Table 1 Patient demographics and ocular characteristics at baseline, by treatment group

	Nepafenac (N=80)	Vehicle (N=80)	p Value
Age (years)			
Mean (SD)	68.1 (8.6)	69.4 (7.6)	0.31
Min, Max	49, 90	53, 84	
Sex, n (%)			
Male	51 (63.8)	44 (55.0)	0.26
Female	29 (36.3)	36 (45.0)	
Race, n (%)			
Asian	6 (7.5)	5 (6.3)	0.97
Black or African-American	1 (1.3)	0 (0.0)	
Native Hawaiian or Other	2 (2.5)	2 (2.5)	
Pacific Islander	0 (0.0)	0 (0.0)	
Other	2 (2.5)	2 (2.5)	
White	69 (86.3)	71 (88.8)	
NPDR classification, n (%)			
Mild NPDR	58 (72.5)	57 (71.3)	1.0
Moderate NPDR	21 (26.3)	22 (27.5)	
Severe NPDR	1 (1.3)	1 (1.3)	
BCVA* (ETDRS letters)			
Mean (SD)	63.3 (12.8)	65.2 (12.1)	0.34
Min, Max	13, 84	28, 84	
CSMT (μm)			
Mean (SD)	268.8 (29.0)	276.8 (23.2)	0.06
Min, Max	182, 371	224, 364	

*Baseline BCVA values based on 79 patients in the nepafenac group and 79 patients in the vehicle group.

Nepafenac=nepafenac ophthalmic suspension, 0.1%; Vehicle=nepafenac ophthalmic suspension, vehicle.

BCVA, best-corrected visual acuity; CSMT, central subfield macular thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, non-proliferative diabetic retinopathy.

Statistical analysis

Details on the statistical analysis can be found in the online supplementary section.

RESULTS

Patient disposition and characteristics

Demographic and baseline characteristics were generally similar between treatment groups for patients in the ITT analysis population (table 1). Mean patient age was 68.1 ± 8.6 years in the nepafenac group and 69.4 ± 7.6 years in the vehicle group. Most patients had non-proliferative diabetic retinopathy (NPDR) that was classified as mild (72.5% in the nepafenac group and 71.3% in the vehicle group). Mean baseline CSMT was $268.8 \pm 29.0 \mu\text{m}$ in the nepafenac group and $276.8 \pm 23.2 \mu\text{m}$ in the vehicle group. Mean baseline BCVA was 63.3 ± 12.8 letters in the nepafenac group and 65.2 ± 12.1 letters in the vehicle group.

MO and central subfield macular thickness

A significantly greater percentage of patients developed MO within 90 days following cataract surgery in the vehicle group ($n=14/80$, 17.5%; 95% CI 9.9% to 27.6%) compared with the nepafenac group ($n=4/80$, 5.0%; 95% CI 1.4% to 12.3%, $p=0.01$). Mean CSMT was increased from baseline at most postsurgical visits in both treatment groups, but increases were markedly lower in the nepafenac group compared with the vehicle group starting at day 30 following cataract surgery (figure 1). CSMT returned to $\pm 10\%$ of baseline within 60 days following cataract surgery in 91.0% ($n=61/67$) of patients in the nepafenac group compared with 55.6% ($n=35/63$) of patients in the vehicle group.

Figure 1 Central subfield macular thickness changes from baseline at each study visit (intent-to-treat population). Mean central subfield thickness was increased from baseline at most postsurgical visits in both treatment groups, but increases were markedly lower in the nepafenac group compared with the vehicle group starting at day 30 following cataract surgery. Sample sizes for the nepafenac group were 73 (day 7), 78 (day 14), 79 (day 30) and 80 (day 60 and day 90). Sample sizes for the vehicle group were 76 (day 7), 79 (day 14) and 80 (day 30, day 60, day 90). BL, baseline.

Postsurgical visual outcomes

Mean BCVA change from preoperative baseline to day 90 following cataract surgery (key secondary end point) was greater in the nepafenac group (17.7 ± 14.6 letters) relative to the vehicle group (14.3 ± 13.9 letters), though the difference was not statistically significant ($p=0.14$).

Mean BCVA change from preoperative baseline to day 90 following cataract surgery was greater in the nepafenac group compared with the vehicle group regardless of whether patients had developed MO at any visit after surgery, though the differences were not statistically significant (table 2).

Among patients who had MO at any visit after surgery, mean BCVA change from preoperative baseline to day 90 following cataract surgery was 16.3 ± 22.1 letters in the nepafenac group and 8.4 ± 15.4 letters in the vehicle group ($p=0.34$). Among patients who did not have MO at any visit after surgery, mean BCVA change from preoperative baseline to day 90 following cataract surgery was 17.8 ± 14.3 letters in the nepafenac group and 15.3 ± 13.5 letters in the vehicle group ($p=0.29$).

From day 7 to day 90 following cataract surgery, BCVA decreased >5 letters in 13.8% ($n=11/80$) of patients in the vehicle group and 6.3% ($n=5/79$) of patients in the nepafenac group. Among patients who developed MO after cataract surgery, BCVA decreased >10 letters from day 7 to any following study visit in 50.0% ($n=7/14$) of patients in the vehicle group and 0.0% ($n=0/4$) of patients in the nepafenac group.

Safety

The incidences of special-interest AEs were generally similar between treatment groups (table 3). Seven cases of punctate

Table 2 BCVA changes from preoperative baseline to day 90 after cataract surgery, by treatment group and macular oedema status (intent-to-treat analysis population)

Treatment group	Total	Mean BCVA change (SD)	95% CI	p Value
MO				
Nepafenac	4	16.3 (22.1)	−18.8 to 51.3	0.34
Vehicle	11	8.4 (15.4)	−2.0 to 18.7	
No MO				
Nepafenac	75	17.8 (14.3)	14.5 to 21.1	0.29
Vehicle	68	15.3 (13.5)	12.0 to 18.5	

Nepafenac=nepafenac ophthalmic suspension, 0.1%; Vehicle=nepafenac ophthalmic suspension, vehicle.
BCVA, best-corrected visual acuity; MO, macular oedema.

keratitis (four and three in the nepafenac and vehicle groups, respectively) and one case of keratitis (vehicle) were reported. Three corneal events were reported (one case each of corneal oedema and disorder in the vehicle group and one of corneal erosion in the vehicle group). Two of the non-serious AEs that led to discontinuation in the nepafenac group were considered to be treatment-related: corneal erosion and allergic dermatitis.

No new safety issues or trends were identified based on review of the incidence, seriousness, intensity, onset, duration, outcome, relationship to treatment or discontinuation due to AEs, or assessments of changes from baseline in corneal staining, intraocular pressure, ocular signs or fundus parameters.

DISCUSSION

This multicentre, randomised, double-masked, vehicle-controlled, parallel-group study validated the hypothesis that nepafenac 0.1% is safe and efficacious for the prevention of MO when used for 90 days following cataract surgery in

patients with DR. A significantly greater percentage of patients in the vehicle group developed MO within 90 days of cataract surgery compared with patients in the nepafenac group.

MO was defined as an increase of 30% or more in CSMT relative to the preoperative baseline measurement. This threshold has been determined to be appropriate for identifying clinically relevant changes in patients and is well above the 10% coefficient of variation associated with OCT repeat testing variability.^{18 19 21} The use of CSMT to determine MO was based on findings from a previous study indicating this measure is more reliable than centre-point macular thickness.²⁰ The beneficial effect of nepafenac in maintaining macular thickness after cataract surgery is also supported by the finding that CSMT was near baseline levels by day 60 following cataract surgery in more than 90% of patients in the nepafenac group compared with only slightly more than half of the patients in the vehicle group. No trends were observed that indicated greater or lesser efficacy among demographic or NPDR severity subgroups, though conclusions cannot be drawn from this analysis due to the small numbers of patients who developed MO in this study.

Visual outcomes were numerically better in the nepafenac group compared with the vehicle group, though none of the observed differences were statistically significant. This lack of statistical significance was likely due to only 67% of the planned total patient population being enrolled after early termination of recruitment (study enrolment was terminated early due to difficulties in patient recruitment). Despite the lack of significance, the results reveal a trend that favours nepafenac compared with vehicle in BCVA change from baseline to day 90 following cataract surgery.

The results of this study are supported by the findings of a previously reported randomised, double-masked, vehicle-controlled clinical trial designed to test the hypothesis that extended treatment with nepafenac 0.1% is safe and efficacious for the prevention of MO following cataract surgery in patients with DR.¹⁸ This is especially notable considering that retinal anatomy was assessed with different types of OCT in each study: SD-OCT in the current study versus time domain OCT (TD-OCT) in the former. A higher percentage of screened patients were excluded from the current study despite the use of similar enrolment criteria across each trial, likely because the greater sensitivity of SD-OCT versus TD-OCT supports an increased ability to detect intraretinal anatomical features, such as cystoid abnormalities, that were cause for exclusion. Inclusion of these patients, with more severe retinopathy, may have allowed for enrolment to be completed and possibly shown a greater difference from vehicle in the end points.

Application of topical ophthalmic nepafenac is a non-invasive approach for preventing MO associated with cataract surgery in patients with diabetes. This is in contrast to the range of currently used off-label treatments for the prevention of MO following surgery, which are all administered by intravitreal injection. These include anti-vascular endothelial growth factor (VEGF) options, such as ranibizumab (LUCENTIS, Genentech, South San Francisco, California, USA), bevacizumab (Avastin, Genentech, South San Francisco, California, USA) and aflibercept, and sustained-release corticosteroid implants that release dexamethasone (OZURDEX, Allergan, Irvine, California, USA).²²

Nepafenac was generally well tolerated in the safety population. Treatment-related AEs in the nepafenac group included four cases of punctate keratitis and one case of allergic dermatitis. Corneal erosion has been labelled as an NSAID class effect, and was therefore targeted as an AE of special interest in the study. As such, exclusion criteria were added to prevent

Table 3 Summary of treatment-emergent adverse events (safety population)

Adverse event category	Nepafenac (N=83)		Vehicle (N=83)	
	N	Per cent	N	Per cent
Patients discontinued due to an AE	4	4.8	7	8.4
Discontinued due to a non-fatal SAE	1	1.2	2	2.4
Discontinued due to a non-serious AE	3	3.6	5	6.0
Treatment-related	2	2.4	2	2.4
Not related to treatment	1	1.2	3	3.6
Patients with at least one treatment-emergent AE related to treatment (ADR)	6	7.2	6	7.2
Most frequent ADRs (incidence of 1% or greater)				
Corneal oedema	0	0.0	1	1.2
Punctate keratitis	4	4.8	3	3.6
Corneal disorder	0	0.0	1	1.2
Corneal erosion	1	1.2	0	0.0
Keratitis	0	0.0	1	1.2
Conjunctival hyperaemia	0	0.0	1	1.2
Eye irritation	0	0.0	1	1.2
Dermatitis allergic	1	1.2	0	0.0

Nepafenac=nepafenac ophthalmic suspension, 0.1%; Vehicle=nepafenac ophthalmic suspension, vehicle.
ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event.

enrolment of patients with compromised corneas.^{23 24} One case of corneal erosion in the nepafenac group was assessed by the investigator as related to study treatment (out of two reported). The patient was discontinued from the study due to this event and the event resolved with treatment within 2 weeks after onset. Nepafenac is currently approved in multiple countries to treat pain and inflammation associated with cataract surgery for the first 2 weeks of the postoperative period. It is also approved in the European Union for the reduction in risk of postoperative MO associated with cataract surgery in patients with diabetes with treatment duration of 60 days. This study confirms that no new safety issues or trends are associated with an extended 90-day course of nepafenac following cataract surgery.

Findings from this study support the benefit of extended treatment with topical ophthalmic nepafenac for the prevention of MO associated with cataract surgery in patients with DR.

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