EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2016
EMA/CHMP/167525/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nevanac

International non-proprietary name: nepafenac

Procedure No. EMEA/H/C/000818/II/0032

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
BCVA	Best-corrected visual acuity
CI	Confidence interval
COX1	Cyclooxygenase 1
COX2	Cyclooxygenase 2
CME	Cystoid macular oedema
CSME	Clinically significant macular oedema
CSMT	Central subfield macular thickness
CSR	Clinical study report
EDTRS	Early Treatment of Diabetic Retinopathy Study
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IOL	Intraocular lens
IOP	Intraocular pressure
ISE	Integrated summary of efficacy
MAA	Marketing Authorization Application
ME	Macular oedema
Max	Maximum
Mg	Milligram
ml	Milliliter
Min	Minimum
N	Number
NNT	Number needed to treat
NPDR	Nonproliferative diabetic retinopathy
NSAID	Nonsteroidal anti-inflammatory drug
OCT	Optical coherence tomography
OR	Odds ratio
PGE2	Prostaglandin E2 (Dinoprostone)
RPE	Retinal pigment epithelium
QD	Once daily (Quaque Die)
QID	Four times daily (Quarter In Die)
SAE	Serious adverse events
SD	Standard deviation
SD OCT	Spectral domain optical coherence tomography
SE	Standard error
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse events
TID	Three times daily (Ter In Die)
TD-OCT	Time domain optical coherence tomography
US or USA	United States of America
VA	Visual acuity
VEGF	Vascular endothelial growth factor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alcon Laboratories (UK) Ltd submitted to the European Medicines Agency on 3 December 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the indication 'reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients' also for the 3 mg/ml strength based on data from the phase III studies C-12-067 and C-12-071. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in SmPC and to update the annexes in line with the latest QRD template. An updated RMP version 7 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Article 8 of the paediatric regulation does not apply to this application, since the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: N/A

Timetable	Actual dates
Start of procedure	3 January 2016
CHMP Rapporteur Assessment Report	3 March 2016
PRAC Rapporteur Assessment Report	4 March 2016
PRAC members comments	10 March 2016
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	17 March 2016
CHMP members comments	21 March 2016
Updated CHMP Rapporteur Assessment Report	28 March 2016
Request for Supplementary Information (RSI)	1 April 2016
CHMP Rapporteur response Assessment Report	27 May 2016
PRAC Rapporteur response Assessment Report	31 May 2016
Comments from PRAC	1 June 2016
Updated PRAC Rapporteur response Assessment Report	N/A
PRAC outcome	9 June 2016
Comments from CHMP	13 June 2016
Updated CHMP Rapporteur response Assessment Report	17 June 2016
Opinion	23 June 2016

2. Scientific discussion

2.1. Introduction

Problem statement

Macular oedema (ME) is a distinct complication of cataract surgery, It is characterised by an abnormal thickening of the macula associated with the accumulation of excess fluid in the extracellular space of the retina or within multiple cyst-like spaces within the macula (ie, cystoid ME [CME]). ME and CME are common causes of poor visual outcome following uneventful cataract surgery.

The prevalence of ME after cataract surgery varies from study to study depending on how it is defined. Whereas only 2% of patients were diagnosed with ME in a study requiring loss of visual acuity to establish the diagnosis, a prevalence of up to 20% has been reported by using fluorescein angiography in other studies. In most cases the oedema is transient, but some patients experience chronic cystic changes in the macula, which may lead to permanent visual loss.

Some groups of patients have a higher risk of new postoperative oedema and the greatest challenges in terms of prophylaxis and treatment: eyes with capsule rupture, patients with a previous diagnosis of epiretinal membrane, uveitis, retinal vein occlusion, retinal detachment, and patients with diabetes, especially those with pre-existing retinopathies (Chu, 2016). Additionally, cataract development occurs at a higher rate and an earlier age in diabetics compared to non-diabetics.

In order to prevent CME after cataract surgery in patients at high risk of developing postoperative CME, corticosteroids are administered commonly due to their anti-inflammatory effects. If topical therapy fails, periocular or intravitreal steroids may be considered. Surgical therapy includes pars plana vitrectomy.

Prostaglandins contribute significantly to the inflammatory processes that result in fluid leakage from perifoveal capillaries into the extracellular space of the macular region. Because topical non-steroidal anti-inflammatory drugs (NSAIDs) block the cyclooxygenase enzymes responsible for prostaglandin production, NSAIDs also may reduce the incidence, duration and severity of CME. NSAID eye drops are thus also currently used in clinical practice.

About the product

Nevanac is an NSAID formulated as ophthalmic suspension. The active ingredient, nepafenac (amfenac amide) is a prodrug that rapidly penetrates the cornea and is coverted to the active metabolite, amfenac, by intraocular hydrolases. Amfenac inhibits both cyclooxygenase COX-1 and COX-2 activity.

Nevanac is available in 2 strengths (1 mg/mL dosed three times daily and 3 mg/mL dosed once daily). This application is seeking approval for the addition of a new indication for Nevanac 3 mg/mL eye drops, suspension: “Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients". The new proposed indication is already approved in the EU for the 1 mg/mL strength.

2.2. Non-clinical aspects

2.2.1. Introduction

Nepafenac (amfenac amide) is a non-steroidal anti-inflammatory and analgesic prodrug. After topical ocular dosing, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to amfenac, a nonsteroidal anti-inflammatory drug. Amfenac inhibits the action of prostaglandin H synthase (cyclooxygenase), an enzyme required for prostaglandin production.

Secondary pharmacology studies demonstrated the ability of nepafenac to suppress retinal neovascularization, while safety pharmacology studies showed that nepafenac had no adverse effect on the central and autonomic nervous, cardiovascular, pulmonary, gastrointestinal, metabolic and renal systems.

The initial toxicology programme included single dose studies (oral route), repeat-dose studies (oral and topical) of up to 6-months duration in several species. Non-clinical data reveal no special hazard for humans based upon the single and repeat-dose studies as well as genotoxicity studies.

2.2.2. Pharmacology

No additional pharmacodynamics studies were conducted in support of this application.

2.2.3. Pharmacokinetics

In support of this submission, the MAH has conducted an ocular uptake and distribution study in rabbits following single (QD) and repeated daily (QD for 8 days) topical ocular doses of Nepafenac 3 mg/mL.

The primary purpose of this study was to determine the distribution of nepafenac and its pharmacologically active metabolite amfenac (AL-6295) to posterior tissues of the eye. The results demonstrated that after topical administration at single or repeated doses, nepafenac 3 mg/mL is distributed locally from the front of the eye to the posterior segments of the eye (retina, choroid). The concentrations of nepafenac in the anterior tissues were at least 2-fold greater than the concentrations observed in the posterior tissues. Similarly, the concentrations of AL-6295 in anterior tissues were generally greater than the concentrations observed in the posterior tissues.

Very low concentrations of nepafenac and AL-6295 were observed in plasma: Cmax of 2.54 and 13.9 ng/mL, respectively, following a single dose; and Cmax of 2.36 and 11.8 ng/mL, respectively, following repeated dosing for 8 days.

Regarding the distribution study, the results demonstrated a concentration gradient for both nepafenac and amfenac (AL-6295) from anterior to posterior segments of the eye. The concentrations in the anterior retinal pigment epithelium (RPE)/choroid and the anterior retina were greater than the concentrations in the posterior RPE/choroid and the posterior retina. Nepafenac concentrations in the anterior RPE/choroid and the anterior retina were approximately 16-and 6-fold higher than the concentrations in the posterior RPE/choroid and the posterior retina, respectively, after single dose. In the same way, AL-6295 concentrations in the anterior RPE/choroid and the anterior retina were approximately 9- and 3-fold higher, respectively, than the concentrations in the posterior RPE/choroid and the posterior retina. In the case of 8 repeated doses, a similar concentration gradient was observed. The anterior RPE/choroid and the anterior retina concentrations were approximately 11-and 4-fold higher (for nepafenac), respectively; and 7-and 4-fold higher (for AL-6295), respectively, than the concentrations in the posterior RPE/choroid and the posterior retina.

2.2.4. Toxicology

No additional toxicology studies were conducted in support of this application.

2.2.5. Ecotoxicity / environmental risk assessment

The Applicant submitted an updated Environmental Risk Assessment. The Predicted Environmental Concentration in surface waters (PEC_{sw}) for nepafenac was 0.00105 µg/L, which is lower than the 0.01 µg/L action value. Furthermore, nepafenac log K_{ow} value was 1.31, lower than the 4.5 threshold for further action. Consequently, nepafenac does not have to be screened for persistence, bioacummulation and toxicity and Phase II environmental fate and effect analysis does not have to be performed.

2.2.6. Discussion on non-clinical aspects

In support of this submission, the Applicant has conducted an ocular uptake and distribution study in rabbits following single and repeated topical ocular doses of Nepafenac 3 mg/mL. The results of this distribution study showed a low systemic exposure of the analytes and no evidence of systemic or ocular tissue accumulation.

No new nonclinical pharmacology and toxicology data have been submitted in this application, which was considered acceptable.

Based on the updated Environmental Risk Assessment no significant increase in environmental exposure further to the use of nepafenac was expected. Nevanac is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

The CHMP concluded that the non-clinical data provided by the MAH were adequate to support this application.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

The applicant confirmed that all clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Safety and Efficacy Studies in Diabetic Subjects Undergoing Cataract Surgery (Nepafenac 3 mg/mL and Nepafenac 1 mg/mL)

Study Identifier/ Study Type	Study Design	Study Population	Treatment Groups	Regions/ countries	Number of Subjects (Primary Efficacy Set)	Dosing Regimen	Dosing Duration
Pivotal Studies with Nepafenac 3 mg/ mL							
C-12-067 Efficacy & Safety	Prospective, Multi-center, Randomized, double masked, parallel-group, vehicle controlled study	Subjects with Type 1 or Type 2 diabetes and non-proliferative retinopathy, 18 years of age and older	Nepafenac 3 mg/mL Vehicle	US, Latin America & Caribbean	298 300	1 drop in study eye, once daily (QD)	92 days
C-12-071 Efficacy & Safety	Prospective, Multi-center, Randomized, double masked, parallel-group, vehicle controlled study	Subjects with Type 1 or Type 2 diabetes and non-proliferative retinopathy, 18 years of age and older	Nepafenac 3 mg/mL Vehicle	US, Europe & Middle East, Latin America & Caribbean, Asia Pacific	289 293	1 drop in study eye, once daily (QD)	92 days
Supportive Studies with Nepafenac 1 mg/ mL							
C-07-43 Efficacy & Safety	Prospective, Multi-center, Randomized, double masked, parallel-group, vehicle controlled study	Subjects with Type 1 or Type 2 diabetes and non-proliferative retinopathy, 18 years of age and older	Nepafenac 1 mg/mL Vehicle	US	125 126	1 drop in study eye, 3 times a day (TID)	92 days
C-09-003* Efficacy & Safety	Prospective, Multi-center, Randomized, double masked, parallel-group, vehicle controlled study	Subjects with Type 1 or Type 2 diabetes and non-proliferative retinopathy, 18 years of age and older	Nepafenac 1 mg/mL Vehicle	US, Europe & Middle East, Asia Pacific	80 80	1 drop in study eye, 3 times a day (TID)	92 days

*Study was terminated early due to recruitment difficulties with ~67% of planned subjects enrolled at the time of study termination

2.3.2. Pharmacokinetics and Pharmacodynamics

No new PK or PD studies were provided.

2.3.3. Discussion and conclusion on clinical pharmacology

No new clinical pharmacology studies have been submitted in this application. This was considered acceptable by the CHMP given the available data generated previously for the 3 mg/ml formulation at the time of the line extension to introduce this strength and the data provided for the 1 mg/ml strength in the same indication.

2.4. Clinical efficacy

The clinical development plan of nepafenac 3 mg/mL for the reduction in risk of postoperative macular oedema in subjects with diabetes included 2 Phase 3 clinical studies (C-12-067 and C-12-071) with the same design.

Additional analyses of Best Corrected Visual Acuity (BCVA) data from studies C-07-43 and C-09-003 conducted with nepafenac 1 mg/mL were submitted as supportive data. These studies were previously submitted and evaluated when this indication was approved for nepafenac 1 mg/mL.

2.4.1. Main studies

C-12-067 - Randomized, Double-Masked, Vehicle Controlled, Clinical Evaluation to Assess the Safety and Efficacy of Nepafenac Ophthalmic Suspension, 0.3% for Improvement in Clinical Outcomes Among Diabetic Subjects Following Cataract Surgery.

C-12-071 - Randomized, Double-Masked, Vehicle Controlled, Clinical Evaluation to Assess the Safety and Efficacy of Nepafenac Ophthalmic Suspension, 0.3% for Improvement in Clinical Outcomes Among Diabetic Subjects Following Cataract Surgery.

Methods

Each study consisted of 9 visits, which included Screening and Randomization (both conducted 2 days to 4 weeks prior to the surgery visit); the cataract surgery visit (Day 0); and 6 postoperative follow-up visits (on Days 1, 7, 14, 30, 60, and 90 [or Early Exit]). Additionally, treatment failure subjects whose ME was not resolved by the Day 90 were followed until Day 120. For these subjects, exit assessments were completed at the Day 120 instead of the Day 90 visit.

Study participants

Key inclusion criteria

1. Subjects must have been 18 years of age and older, must have had a cataract, and were planning to undergo cataract extraction by phacoemulsification with the implantation of a posterior chamber IOL into the lens capsule.

2. History of Type 1 or 2 diabetes and NPDR (mild, moderate, or severe) in the study eye as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale and confirmed by the reading centre.

3. Subjects must have had a preoperative screening BCVA of 73 letters or worse (as assessed using the Early Treatment of Diabetic Retinopathy Study [ETDRS] chart) in the study eye.

Key exclusion criteria

1. Pre-existing ME in the study eye as determined by SD OCT and confirmed by the reading center (CSMT of ≥ 320 µm Spectralis or ≥ 300 µm Cirrus).

2. Signs of vitreomacular traction or epiretinal membrane in the study eye as detected by SD OCT or fundus examination per the reading center or Investigator.

3. History in the study eye of retinal detachment, ischemic maculopathy (may have been confirmed by fluorescein angiography if necessary), central retinal vein occlusion, branch retinal vein occlusion, central retinal artery occlusion, or branch retinal artery occlusion, exudative (wet) age related macular degeneration, chronic or recurrent inflammatory eye disease (eg, iritis, scleritis, uveitis, iridocyclitis).

4. Prior procedures in the study eye: macular surgeries (eg, macular hole, epiretinal membrane removal), panretinal photocoagulation, corneal transplant, intraocular surgery or penetrating ocular trauma (including traumatic cataract), focal photocoagulation for the treatment of diabetic ME within 6 months of the preoperative visit (peripheral retina treatment for retinal tear or lattice degeneration was permitted).

Subjects were to be excluded from participation if they used:

- Intraocular/periocular steroids or antivascular endothelial growth factor therapy in the study eye within 6 months prior to surgery
- Systemic steroids (excluding nasal, inhaled, or topical dermal steroids) or topical ocular steroids in the study eye within 14 days prior to surgery
- Topical ocular NSAIDs in the study eye or systemic NSAIDs (except aspirin at a maximal dose of 325 mg) within 7 days prior to surgery
- Daily doses of topical ocular NSAIDs or steroids in the nonstudy eye 1 day prior to surgery
- Topical ophthalmic prostaglandins (eg, Travatan, Xalatan) in the study eye within 4 days prior to surgery
- Supplemental niacin (≥ 3 g/day), or medications that had known or suspected retinal toxicities (eg, hydroxychloroquinine and phenothiazines).

Treatments

Eligible subjects were randomized to receive either Nepafenac 0.3% or Vehicle; the assigned investigational product was to be instilled in the study once daily beginning the day prior to surgery and concluding on Day 90 post-surgery. Subjects also received 1 drop of study drug 30 to 120 minutes prior to the scheduled cataract surgery on Day 0. All subjects were to receive OMNIPRED or alternate prednisolone eye drops for 4 weeks post surgery.

Objectives

The objective was to demonstrate the superiority of Nepafenac 0.3% dosed once daily relative to vehicle based upon clinical outcomes following cataract surgery in subjects with diabetic retinopathy.

Outcomes/endpoints

The assessment was conducted at Screening, and Days 1, 7, 14, 30, 60 and 90 (or Day 120, if applicable, or Early Exit).

Primary Efficacy Variable: The proportion of subjects who developed macular oedema (ME) within 90 days following cataract surgery. ME was defined as an increase in CSMT of ≥ 30% relative to the preoperative baseline measurement as measured by SD-OCT

Secondary Efficacy Variable:

- The proportion of subjects with improvements in BCVA of ≥ 15 letters from the preoperative baseline to Day 14 and maintained through Day 90
- The proportion of subjects with improvements in BCVA of ≥ 15 letters from the preoperative baseline to Day 90
- The proportion of subjects with improvements in BCVA of ≥ 15 letters from the preoperative baseline to Day 60

- Additional secondary endpoints:
    - The proportion of subjects with a > 5-letter loss in BCVA from Day 7 to any visit
    - The proportion of subjects with a >10-letter loss in BCVA from Day 7 to any visit

Supportive endpoints:

- The proportion of subjects with treatment failure at each visit. Treatment failure was defined as an increase in CSMT of ≥ 30% from the preoperative baseline as measured by SD-OCT
- The change from baseline in CSMT
- The percent change from baseline in CSMT
- The change from baseline in macular volume
- The percent change from baseline in macular volume
- The mean change in BCVA from baseline
- The mean change in BCVA from Day 7

Sample size

Approximately 590 subjects were planned for randomization in each study in order to obtain 560 evaluable subjects. An evaluable sample size of 560 subjects was expected to provide approximately 90% power to detect a 14% difference between Nepafenac 0.3% and Vehicle in the proportion of subjects with BCVA improvements of ≥ 15 letters from the preoperative baseline to Day 14 and maintained through Day 90. The proportion of subjects in the Vehicle group who met this efficacy endpoint was expected to be approximately 45%.

This sample size also provides greater than 99% power to detect a difference of at least 13% in the endpoint of the incidence of ME (assuming this to be 18% in the Vehicle arm).

Randomisation

Enrolled subjects were randomized (1:1) to Nepafenac 3 mg/mL or Vehicle. Randomization was stratified by NPDR grade. The Interactive Response Technology was used to monitor the enrolment by severity to ensure that at least 50% of the randomized subjects had moderate or severe NPDR.

Blinding (masking)

Nepafenac 0.3% and Vehicle were packaged and labelled identically. The dispensing, collection and administration of the investigational product was made at each investigational centre by designated staff who were not involved in the assessment of any primary or secondary efficacy variables.

Statistical methods

The full analysis set (FAS) included all randomized subjects who completed implant surgery and had at least 1 on-therapy postsurgical visit. This analysis set was considered primary for the evaluation of efficacy.

The per protocol (PP) analysis set included all subjects in the FAS who had no major protocol violations.

Finally, the safety analysis set included all subjects who were exposed or were deemed exposed (ie, discontinued the study prior to surgery, but either returned an opened bottle of study drug or failed to return study drug) to treatment.

Analysis of Efficacy

For the evaluation of the proportion of subjects who developed ME within 90 days following cataract surgery, a logistic regression model, which included factors for treatment and the stratification variable of retinopathy severity, was performed to assess treatment group differences. An estimate of the odds ratio, the associated 95% CI, and p-value were provided.

The evaluation of the proportion of subjects with BCVA improvements of ≥ 15 letters from the preoperative baseline to Day 14 and maintained through Day 90 was based on a binary outcome (positive or negative), which was derived using the change from the preoperative baseline in BCVA at Days 14, 30, 60, and 90. A positive outcome required an improvement from the preoperative baseline in BCVA of ≥ 15 letters at all 4 time points; any other outcome was considered negative. A subject with missing BCVA values at 1 or more time points was considered to have had a negative outcome. A logistic regression model, which included terms for treatment and the stratification variable of retinopathy severity, was employed for the analysis of this endpoint. The primary inference was based on the odds ratio of a positive outcome. An estimate of the odds ratio, the associated 95% confidence interval (CI), and p-value were provided, along with the difference in proportions and the associated CIs. A similar approach was employed to analyze the remaining secondary efficacy endpoints associated with changes in BCVA.

The analyses of the supportive endpoints were descriptive in nature. A logistic regression model, which included terms for treatment and the stratification variable of retinopathy severity, was employed for the analysis of the proportion of subjects who were treatment failures. Endpoints related to changes or percent changes from baseline were analyzed using mixed model repeated measures analysis, with terms for the corresponding baseline measurements (BCVA, macular thickness, or macular volume), treatment, stratification factor (retinopathy severity), study visit, and treatment-by-study visit interaction; the analysis of the change in BCVA from Day 7 was adjusted for the Day 7 BCVA measurement instead of for the baseline BCVA measurement. An unstructured variance-covariance matrix was used to account for within-subject correlation in the repeated measures. In case of model nonconvergence, a simpler variance-covariance matrix was employed. Within-treatment estimates of the mean changes from baseline by visit and the associated 95% CIs were provided, along with an estimate of the differences in means by visit and the associated 95% CIs were provided.

Results

Participant flow

- **Study 067:** A total of 615 subjects were randomized, including 308 subjects in the Nepafenac 0.3% group and 307 subjects in the Vehicle group; 12 of the randomized subjects (7 in the Nepafenac 0.3% group and 5 in the Vehicle group) did not receive treatment.

Table 2 Subject disposition in study 067

	Nepafenac n (%)	Vehicle n (%)	Overall n (%)
Total enrolled [a]			881
Screen failures			253
Discontinued prior to randomization			13
Randomized	308	307	615
As Randomized			
Treated	301 (97.7)	302 (98.4)	603 (98.0)
Completed the study [b]	296 (96.1)	286 (93.2)	582 (94.6)
Discontinued from study	12 (3.9)	21 (6.8)	33 (5.4)
Screen failure	0 (0)	0 (0)	0 (0)
Adverse event	0 (0)	4 (1.3)	4 (0.7)
Death	1 (0.3)	4 (1.3)	5 (0.8)
Lost to follow-up	0 (0)	3 (1.0)	3 (0.5)
Non-compliance with study drug	0 (0)	1 (0.3)	1 (0.2)
Physician decision	1 (0.3)	1 (0.3)	2 (0.3)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol violation	0 (0)	0 (0)	0 (0)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)
Withdrawal by subject	1 (0.3)	2 (0.7)	3 (0.5)
Other	9 (2.9)	6 (2.0)	15 (2.4)
As Treated			
Treated	301	302	603
Completed the study [b]	296 (98.3)	286 (94.7)	582 (96.5)
Discontinued from study	5 (1.7)	16 (5.3)	21 (3.5)
Screen failure	0 (0)	0 (0)	0 (0)
Adverse event	0 (0)	3 (1.0)	3 (0.5)
Death	1 (0.3)	4 (1.3)	5 (0.8)
Lost to follow-up	0 (0)	3 (1.0)	3 (0.5)
Non-compliance with study drug	0 (0)	1 (0.3)	1 (0.2)
Physician decision	1 (0.3)	1 (0.3)	2 (0.3)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol violation	0 (0)	0 (0)	0 (0)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)
Withdrawal by subject	0 (0)	2 (0.7)	2 (0.3)
Other	3 (1.0)	2 (0.7)	5 (0.8)

Nepafenac = Nepafenac Ophthalmic Suspension, 0.3%
Vehicle = Nepafenac Ophthalmic Suspension Vehicle
12 subject(s) were randomized but were not treated.
Percentages in 'As Randomized' section based on number of subjects randomized by treatment group while percentages in 'As Treated' section based on number of subjects treated by treatment group.
[a] Total enrolled = Total number of subjects consented
[b] Completed the study indicated by subject's exit status on eCRF exit form.

- **Study 071:** A total of 605 subjects were randomized, including 301 subjects in the Nepafenac 0.3% group and 304 subjects in the Vehicle group; 17 of the randomized subjects (8 in the Nepafenac 0.3% group and 9 in the Vehicle group) did not receive treatment.

Table 3 Subject disposition in Study 071

	Nepafenac n (%)	Vehicle n (%)	Overall n (%)
Total enrolled [a]			819
Screen failures			191
Discontinued prior to randomization			23
Randomized	301	304	605
As Randomized			
Treated	293 (97.3)	295 (97.0)	588 (97.2)
Completed the study [b]	277 (92.0)	292 (96.1)	569 (94.0)
Discontinued from study	24 (8.0)	12 (3.9)	36 (6.0)
Screen failure	0 (0)	0 (0)	0 (0)
Adverse event	3 (1.0)	2 (0.7)	5 (0.8)
Death	0 (0)	2 (0.7)	2 (0.3)
Lost to follow-up	8 (2.7)	1 (0.3)	9 (1.5)
Non-compliance with study drug	0 (0)	0 (0)	0 (0)
Physician decision	1 (0.3)	0 (0)	1 (0.2)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol violation	0 (0)	0 (0)	0 (0)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)
Withdrawal by subject	6 (2.0)	1 (0.3)	7 (1.2)
Other	6 (2.0)	6 (2.0)	12 (2.0)
As Treated			
Treated	293	295	588
Completed the study [b]	277 (94.5)	292 (99.0)	569 (96.8)
Discontinued from study	16 (5.5)	3 (1.0)	19 (3.2)
Screen failure	0 (0)	0 (0)	0 (0)
Adverse event	3 (1.0)	1 (0.3)	4 (0.7)
Death	0 (0)	1 (0.3)	1 (0.2)
Lost to follow-up	8 (2.7)	0 (0)	8 (1.4)
Non-compliance with study drug	0 (0)	0 (0)	0 (0)
Physician decision	0 (0)	0 (0)	0 (0)
Pregnancy	0 (0)	0 (0)	0 (0)
Protocol violation	0 (0)	0 (0)	0 (0)
Study terminated by sponsor	0 (0)	0 (0)	0 (0)
Withdrawal by subject	5 (1.7)	0 (0)	5 (0.9)
Other	0 (0)	1 (0.3)	1 (0.2)

Nepafenac = Nepafenac Ophthalmic Suspension, 0.3%
Vehicle = Nepafenac Ophthalmic Suspension Vehicle
12 subject(s) were randomized but were not treated.
Percentages in 'As Randomized' section based on number of subjects randomized by treatment group while percentages in 'As Treated' section based on number of subjects treated by treatment group.
[a] Total enrolled = Total number of subjects consented
[b] Completed the study indicated by subject's exit status on eCRF exit form.

Recruitment

Study C-12-067 was conducted mainly in the US (~84% of the subjects from US sites) and additional sites in Latin America and the Caribbean. Study C-12-071 was conducted globally, with sites in Asia, Australia, Europe, Latin America & Caribbean, Middle East and the US. Of the 582 subjects contributing to the primary analysis set (FAS) in Study C-12-071, 172 subjects (29.6%) were from 6 countries (Austria, France, Germany, Italy, Spain and Hungary) in the EU.

Conduct of the study

Both studies were amended to exclude the use of silicone IOLs for implantation.

Study 067 was amended to include Latin America and the Caribbean to increase the number of investigational centres (from 55 to 70), and to update the storage requirements for the investigational products. It was also clarified that alternate forms of prednisolone eye drops could have been used as required concomitant medication in the study if OMNIPRED was not marketed or available in the applicable country and that the Day 120 follow-up visit would serve as the Exit Visit for subjects with treatment failures whose ME was unresolved by the Day 90 visit.

Study 071 was amended to make clarifications regarding the dosing rationale, to prohibit the concomitant use of contact lenses, and to exclude subjects with known medical histories of intolerance to fluorescein.

Baseline data

The study populations (FAS) of C-12-067 and C-12-071 were similar in terms of age, gender, ethnicity and iris colour, as described in Table below.

Table 4 Demographic statistics (Full Analysis Set)

	C-12-067			C-12-071			Pooled		
	Nepafenac (N = 298)	Vehicle (N = 300)	Overall (N = 598)	Nepafenac (N = 289)	Vehicle (N = 293)	Overall (N = 582)	Nepafenac (N = 587)	Vehicle (N = 593)	Overall (N = 1180)
Age (Years)									
n	298	300	598	289	293	582	587	593	1180
Mean (SD)	66.8 (8.5)	66.8 (8.3)	66.8 (8.4)	67.7 (8.5)	68.1 (8.4)	67.9 (8.4)	67.2 (8.5)	67.4 (8.3)	67.3 (8.4)
Median	67.0	66.0	67.0	67.0	68.0	68.0	67.0	67.0	67.0
(Min, Max)	(30, 93)	(37, 88)	(30, 93)	(41, 94)	(37, 89)	(37, 94)	(30, 94)	(37, 89)	(30, 94)
Age Group, n (%)									
18-64	100 (33.6)	110 (36.7)	210 (35.1)	101 (34.9)	84 (28.7)	185 (31.8)	201 (34.2)	194 (32.7)	395 (33.5)
≥ 65	198 (66.4)	190 (63.3)	388 (64.9)	188 (65.1)	209 (71.3)	397 (68.2)	386 (65.8)	399 (67.3)	785 (66.5)
≥ 65 to <75	145 (48.7)	137 (45.7)	282 (47.2)	120 (41.5)	141 (48.1)	261 (44.8)	265 (45.1)	278 (46.9)	543 (46.0)
≥ 75 to <85	50 (16.8)	47 (15.7)	97 (16.2)	64 (22.1)	64 (21.8)	128 (22.0)	114 (19.4)	111 (18.7)	225 (19.1)
≥ 85 to <95	3 (1.0)	6 (2.0)	9 (1.5)	4 (1.4)	4 (1.4)	8 (1.4)	7 (1.2)	10 (1.7)	17 (1.4)
Sex, n (%)									
Male	140 (47.0)	134 (44.7)	274 (45.8)	140 (48.4)	144 (49.1)	284 (48.8)	280 (47.7)	278 (46.9)	558 (47.3)
Female	158 (53.0)	166 (55.3)	324 (54.2)	149 (51.6)	149 (50.9)	298 (51.2)	307 (52.3)	315 (53.1)	622 (52.7)
Race, n (%)									
White	220 (73.8)	231 (77.0)	451 (75.4)	174 (60.2)	169 (57.7)	343 (58.9)	394 (67.1)	400 (67.5)	794 (67.3)
Black or African American	50 (16.8)	44 (14.7)	94 (15.7)	13 (4.5)	11 (3.8)	24 (4.1)	63 (10.7)	55 (9.3)	118 (10.0)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0.2)	1 (0.2)	0 (0)	1 (0.1)
Asian	5 (1.7)	5 (1.7)	10 (1.7)	26 (9.0)	34 (11.6)	60 (10.3)	31 (5.3)	39 (6.6)	70 (5.9)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.3)	1 (0.2)	0 (0)	1 (0.3)	1 (0.2)	0 (0)	2 (0.3)	2 (0.2)
Multi-racial	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	2 (0.3)	2 (0.3)	0 (0)	2 (0.2)
Other	23 (7.7)	19 (6.3)	42 (7.0)	73 (25.3)	78 (26.6)	151 (25.9)	96 (16.4)	97 (16.4)	193 (16.4)
Ethnicity, n (%)									
Hispanic or Latino	120 (40.3)	126 (42.0)	246 (41.1)	118 (40.8)	128 (43.7)	246 (42.3)	238 (40.5)	254 (42.8)	492 (41.7)
Not Hispanic or Latino	178 (59.7)	174 (58.0)	352 (58.9)	171 (59.2)	165 (56.3)	336 (57.7)	349 (59.5)	339 (57.2)	688 (58.3)
Iris Color, n (%)									
Blue	53 (17.8)	71 (23.7)	124 (20.7)	35 (12.1)	39 (13.3)	74 (12.7)	88 (15.0)	110 (18.5)	198 (16.8)
Brown	213 (71.5)	196 (65.3)	409 (68.4)	196 (67.8)	211 (72.0)	407 (69.9)	409 (69.7)	407 (68.6)	816 (69.2)
Green	6 (2.0)	9 (3.0)	15 (2.5)	20 (6.9)	21 (7.2)	41 (7.0)	26 (4.4)	30 (5.1)	56 (4.7)
Grey	2 (0.7)	3 (1.0)	5 (0.8)	10 (3.5)	6 (2.0)	16 (2.7)	12 (2.0)	9 (1.5)	21 (1.8)
Hazel	24 (8.1)	20 (6.7)	44 (7.4)	26 (9.0)	15 (5.1)	41 (7.0)	50 (8.5)	35 (5.9)	85 (7.2)
Other	0 (0)	1 (0.3)	1 (0.2)	2 (0.7)	1 (0.3)	3 (0.5)	2 (0.3)	2 (0.3)	4 (0.3)

Nepafenac = Nepafenac Ophthalmic Suspension, 0.3%
Vehicle = Nepafenac Ophthalmic Suspension Vehicle
SD = Standard deviation
N = Number of subjects in treatment group and analysis set
n = Number of subjects in category

There were no meaningful differences between treatment groups with regards to any baseline characteristic, as outlined in Table 5 below.

Table 5 Baseline characteristics (Full Analysis Set)

	C-12-067			C-12-071			Pooled		
	Nepafenac (N = 298)	Vehicle (N = 300)	Overall (N = 598)	Nepafenac (N = 289)	Vehicle (N = 293)	Overall (N = 582)	Nepafenac (N = 587)	Vehicle (N = 593)	Overall (N = 1180)
Central Subfield Macular Thickness									
n	298	299	597	289	292	581	587	591	1178
Mean (SD)	245.4 (24.2)	247.6 (25.0)	246.5 (24.6)	246.0 (25.0)	247.8 (23.4)	246.9 (24.2)	245.7 (24.6)	247.7 (24.2)	246.7 (24.4)
Median	247.0	246.0	247.0	248.0	247.5	248.0	248.0	247.0	247.0
(Min, Max)	(128, 299)	(164, 299)	(128, 299)	(164, 299)	(182, 299)	(164, 299)	(128, 299)	(164, 299)	(128, 299)
BCVA									
n	298	300	598	289	293	582	587	593	1180
Mean (SD)	62.0 (12.1)	63.0 (11.0)	62.5 (11.6)	59.6 (14.0)	59.8 (12.4)	59.7 (13.2)	60.8 (13.1)	61.4 (11.8)	61.1 (12.5)
Median	65.5	65.5	65.5	64.0	63.0	63.0	65.0	65.0	65.0
(Min, Max)	(0, 76)	(0, 74)	(0, 76)	(0, 77)	(0, 73)	(0, 77)	(0, 77)	(0, 74)	(0, 77)
Retinopathy Severity n (%)									
Mild	40 (13.4)	44 (14.7)	84 (14.0)	29 (10.0)	33 (11.3)	62 (10.7)	69 (11.8)	77 (13.0)	146 (12.4)
Moderate	255 (85.6)	253 (84.3)	508 (84.9)	260 (90.0)	257 (87.7)	517 (88.8)	515 (87.7)	510 (86.0)	1025 (86.9)
Severe	3 (1.0)	3 (1.0)	6 (1.0)	0 (0)	3 (1.0)	3 (0.5)	3 (0.5)	6 (1.0)	9 (0.8)

Numbers analysed

The primary efficacy analysis set was the FAS. The PP analysis set was supportive.

C-12-067

Table 6 Subjects evaluable by Analysis Set

	Nepafenac (N=308) n (%)	Vehicle (N=307) n (%)	Overall (N=615) n (%)
Safety Analysis Set	301 (97.7)	302 (98.4)	603 (98.0)
Full Analysis Set	298 (96.8)	300 (97.7)	598 (97.2)
Per-protocol Analysis Set	279 (90.6)	278 (90.6)	557 (90.6)

Nepafenac = Nepafenac Ophthalmic Suspension, 0.3%
Vehicle = Nepafenac Ophthalmic Suspension Vehicle
N = Number of subjects in treatment group
n = Number of subjects in category

C-12-071

Table 7 Subjects Evaluable by Analysis Set

	Nepafenac (N=301) n (%)	Vehicle (N=304) n (%)	Overall (N=605) n (%)
Safety Analysis Set	293 (97.3)	295 (97.0)	588 (97.2)
Full Analysis Set	289 (96.0)	293 (96.4)	582 (96.2)
Per-protocol Analysis Set	275 (91.4)	277 (91.1)	552 (91.2)

Nepafenac = Nepafenac Ophthalmic Suspension, 0.3%
Vehicle = Nepafenac Ophthalmic Suspension Vehicle
N = Number of subjects in treatment group
n = Number of subjects in category

Outcomes and estimation

a) OCT parameters

Development of Macular Oedema (Primary Endpoint)

Primary efficacy analyses of both studies C-12-067 and C-12-071 demonstrated that Nepafenac 3 mg/ mL significantly reduced the risk of ME development following cataract surgery compared to vehicle. The results of per protocol analysis were also consistent between the studies.

- **C-12-067**

A significantly lower proportion of subjects in the Nepafenac 3 mg/ mL group (2.3%) developed ME within 90 days following surgery compared to the vehicle group (17.3%; p< 0.001). The model-based estimate of the difference (adjusting for baseline retinopathy stratum) was 14.9.

Table 8 Analysis of Percentage of Subjects who Developed Macular Oedema (Full Analysis Set)

	Nepafenac (N = 298)	Vehicle (N = 300)
n (%)	7 (2.3)	52 (17.3)
SE	0.9	2.2
Difference (95% CI)		-14.9 (-21.6, -9.3)
Odds Ratio (SE)		0.1 (0.1)
95% CI		(0.1, 0.3)
p-value		<0.001

Table 9 Analysis of Percentage of Subjects who Developed Macular Oedema (Per-Protocol Set)

	Nepafenac (N = 279)	Vehicle (N = 278)
n (%)	6 (2.2)	45 (16.2)
SE	0.9	2.2
Difference (95% CI)		-13.6 (-20.6, -7.9)
Odds Ratio (SE)		0.1 (0.1)
95% CI		(0.1, 0.3)
p-value		<0.001

- **C-12-071**

A significantly lower proportion of subjects in the Nepafenac 3 mg/ mL group (5.9%) developed ME within 90 days following surgery compared to vehicle group (14.3%; p = 0.001). The model-based estimate of the difference (adjusting for baseline retinopathy stratum) was 6.8.

Table 10 Analysis of Percentage of Subjects who Developed Macular Oedema (Full Analysis Set)

	Nepafenac (N = 289)	Vehicle (N = 293)
n (%)	17 (5.9)	42 (14.3)
SE	1.4	2.0
Difference (95% CI)		-6.8 (-14.2, -0.8)
Odds Ratio (SE)		0.4 (0.1)
95% CI		(0.2, 0.7)
p-value		0.001

Table 11 Analysis of Percentage of Subjects who Developed Macular Oedema (Per-Protocol Set)

	Nepafenac (N = 275)	Vehicle (N = 277)
n (%)	12 (4.4)	36 (13.0)
SE	1.2	2.0
Difference (95% CI)		-7.6 (-15.1, -1.7)
Odds Ratio (SE)		0.3 (0.1)
95% CI		(0.2, 0.6)
p-value		<0.001

Nepafenac = Nepafenac Ophthalmic Suspension, 0.3%; Vehicle = Nepafenac Ophthalmic Suspension Vehicle
N = Number of subjects in treatment group and analysis set; n = Number of subjects with event; SE = Standard error; CI = Confidence interval
Difference (percentage, Nepafenac - Vehicle) and associated CI derived based on Logistic regression model estimates using Miettinen and Nurminen method. Odds ratio is odds of event on Nepafenac divided by odds of event on Vehicle. Percentage of event, odds ratio, CI, and p-value were based on Logistic regression model with terms for treatment and retinopathy severity.

Supportive endpoints

Mean change and percentage change from pre-operative baseline in CSMT to each visit

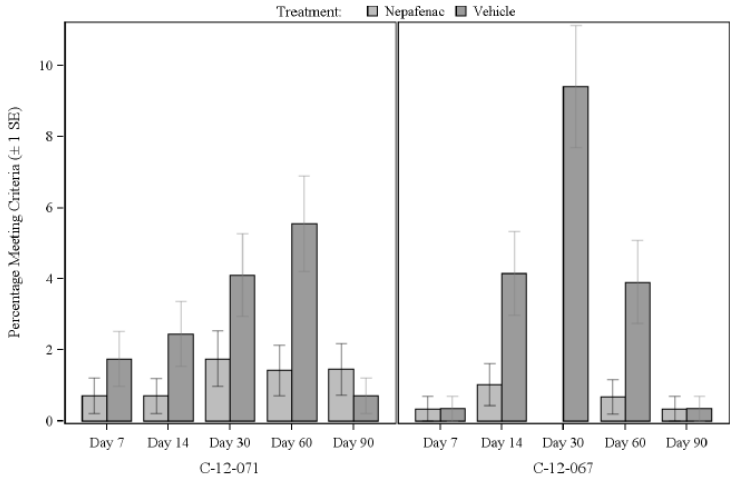
In both studies, subjects in Nepafenac 3 mg/mL group had less increase in CSMT from pre-operative baseline compared to the vehicle group at all post-operative visits from Day 7 to Day 90 ($p < 0.05$ at all visits in both studies).

Table 12: Pre-operative Baseline and Change from Baseline in CSMT by Visit (Full Analysis Set)

	C-12-067			C-12-071		
	Nepafenac (N=298) mean	Vehicle (N=300) mean	Difference: Nep-Veh (p-value)	Nepafenac (N=289) mean	Vehicle (N=293) mean	Difference: Nep-Veh (p-value)
Baseline	245.4	247.6	-	246.0	247.8	-
Day 7	0.6	3.4	-2.9 (p=0.007)	1.6	4.8	-3.2 (p=0.042)
Day 14	4.6	15.4	-10.8 (p<0.001)	6.7	16.6	-9.9 (p<0.001)
Day 30	6.7	32.9	-26.2 (p<0.001)	10.5	26.4	-15.9 (p<0.001)
Day 60	6.9	28.8	-21.9 (p<0.001)	12.9	32.8	-19.9 (p<0.001)
Day 90	8.5	20.4	-11.9 (p<0.001)	12.3	20.8	-8.5 (p=0.003)

Source tables: Table 11-16 in C-12-067 CSR and Table 11-16 in C-12-071 CSR

Figure 1: Percentage of Subjects who Developed Macular Oedema by Visit (Full Analysis Set)

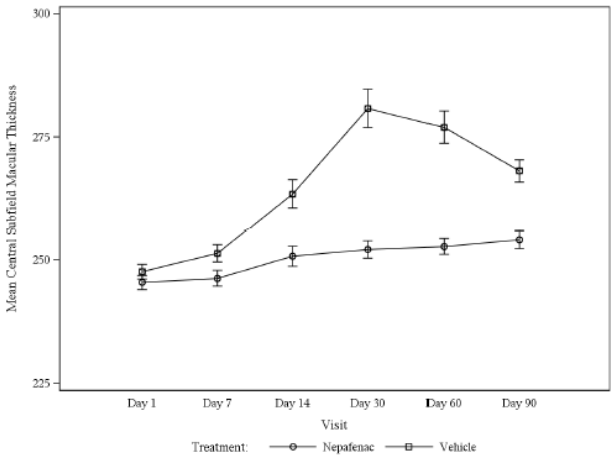


Mean Central Subfield Macular Thickness

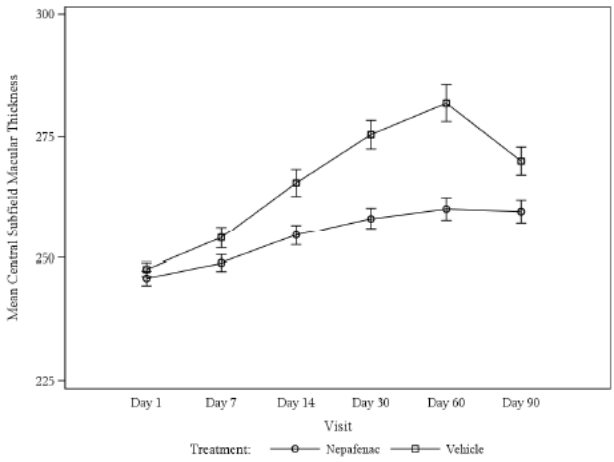
The results were consistent in both studies in terms of the beneficial effects of Nepafenac 3mg/mL; however the peak increase in mean CSMT in the vehicle group was seen to occur at Day 30 in C-12-067 while in C-12-071 it was observed at Day 60. In both studies, the mean CSMT in Vehicle group decreased below the peak levels by Day 90, however it did not returned to the preoperative baseline levels.

Figure 2 Mean Central Subfield Macular Thickness (± 1 SE) by Visit (Full Analysis Set)

Study 067



Study 071



b) BCVA parameters

- **C-12-067**

A significantly higher proportion of subjects achieved clinically relevant improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and maintained through Day 90 in the Nepafenac 3 mg/mL group (61.7%) compared to the vehicle group (43%, p< 0.001). Nepafenac 3 mg/ mL was also superior to Vehicle for all other secondary endpoints (p < 0.05 for all).

Table 13 Analysis of Percentage of Subjects with BCVA Improvement of ≥ 15 Letters from Baseline to Day 14 and maintained through Day 90 (Full Analysis Set)

	Nepafenac (N = 298)	Vehicle (N = 300)
n (%)	184 (61.7)	129 (43.0)
SE	2.8	2.9
Difference (95% CI)		18.7 (8.9, 28.3)
Odds Ratio (SE)		2.1 (0.4)
95% CI		(1.5, 3.0)
p-value		<0.001

Table 14 Analysis of Percentage of Subjects with BCVA Improvement of ≥ 15 Letters from Baseline to Day 14 and maintained through Day 90 (Per Protocol)

	Nepafenac (N = 279)	Vehicle (N = 278)
n (%)	158 (56.6)	99 (35.6)
SE	3.0	2.9
Difference (95% CI)		21.0 (10.7, 30.9)
Odds Ratio (SE)		2.4 (0.4)
95% CI		(1.7, 3.3)
p-value		<0.001

- **C-12-071**

The proportion of subjects who achieved clinically relevant improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and maintained through Day 90 in Nepafenac 3 mg/ mL group (48.8%) was not significantly different from the vehicle group (50.5%, p = 0.671).

Table 15 Analysis of Percentage of Subjects with BCVA Improvement of ≥ 15 Letters from Baseline to Day 14 and Maintained through Day 90 (Full Analysis Set)

	Nepafenac (N = 289)	Vehicle (N = 293)
n (%)	141 (48.8)	148 (50.5)
SE	2.9	2.9
Difference (95% CI)		-1.8 (-12.6, 9.2)
Odds Ratio (SE)		0.9 (0.2)
95% CI		(0.7, 1.3)
p-value		0.671

Table 16 Analysis of Percentage of Subjects with BCVA Improvement of ≥ 15 Letters from Baseline to Day 14 and Maintained through Day 90 (Per Protocol)

	Nepafenac (N = 275)	Vehicle (N = 277)
n (%)	128 (46.5)	119 (43.0)
SE	3.0	3.0
Difference (95% CI)		3.5 (-7.8, 14.8)
Odds Ratio (SE)		1.2 (0.2)
95% CI		(0.8, 1.6)
p-value		0.400

The difference between treatment groups was not significant for other secondary endpoints; numerical difference in favour of Nepafenac 3 mg/ mL was observed for BCVA improvement of ≥ 15 letters from Preoperative Baseline to Day 60 (68.9% subjects for Nepafenac 3 mg/ mL compared to 62.1% for Vehicle, p = 0.092).

Analysis of Change from Baseline in BCVA (Full Analysis Set)

Table 17 Study 067: Analysis of Change from Baseline in BCVA (Full Analysis Set)

	Nepafenac (N = 298)	Vehicle (N = 300)
Baseline		
n	298	300
Mean (SD)	62.0 (12.1)	63.0 (11.0)
Day 90		
n	291	287
Mean (SD)	84.4 (6.2)	82.7 (6.8)
Change from Baseline [a]		
Mean (SE)	22.0 (0.5)	20.4 (0.5)
95% CI	(21.1, 22.9)	(19.5, 21.3)
Difference in Change from Baseline [b]		
Mean (SE)		1.7 (0.5)
95% CI		(0.6, 2.7)
P-value		0.002

Table 18 Study 071: Analysis of Change from Baseline in BCVA (Full Analysis Set)

	Nepafenac (N = 289)	Vehicle (N = 293)
Baseline		
n	289	293
Mean (SD)	59.6 (14.0)	59.8 (12.4)
Day 90		
n	275	285
Mean (SD)	82.4 (6.7)	80.9 (7.2)
Change from Baseline [a]		
Mean (SE)	23.0 (0.6)	21.8 (0.6)
95% CI	(21.9, 24.2)	(20.7, 22.9)
Difference in Change from Baseline [b]		
Mean (SE)		1.2 (0.6)
95% CI		(0.0, 2.4)
P-value		0.046

Only Study 067 showed a significant difference between groups (18.7%; p<0.001) in the percentage of patients with an increase in BCVA of more than 15 letters. In Study 071 the difference between Nepafenac and Vehicle groups was -1.8% (p=0.671). No difference was shown in the remaining visual acuity-related measures.

No significant differences between groups were observed in mean BCVA change and ultimate BCVA was excellent in both groups at the end of the studies.

Ancillary analyses

Subgroup analyses were performed for the primary and secondary efficacy endpoints. The observed efficacy of Nepafenac 3 mg/mL for reducing the risk of ME occurrence was consistent across all subgroups defined by demographic factors (age, gender, race and iris color) and baseline retinopathy severity, in C-12-067 and C-12-071.

In C-12-067, the observed efficacy of Nepafenac 3 mg/mL in improving visual outcomes was consistent across all subgroups defined by the demographics factors and baseline retinopathy severity. In C-12-071, there was no consistency in any subgroup with the overall results; directional inconsistencies were noted with some results in favour of Nepafenac 3 mg/mL and some in favour of Vehicle.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19 Summary of Efficacy for trial C-12-067

Title: Randomized, Double-Masked, Vehicle Controlled, Clinical Evaluation to Assess the Safety and Efficacy of Nepafenac Ophthalmic Suspension, 0.3% for Improvement in Clinical Outcomes Among Diabetic Subjects Following Cataract Surgery (conducted in the United States, and in Latin America and the Caribbean).			
Study identifier	**C-12-067**		
Design	Randomised, double-blind, vehicle-controlled.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		90 days not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Nepafenac 3mg/ml		1 drop once daily for 90 days, 308 patients randomised
	Vehicle		1 drop once daily for 90 days, 307 patients randomised
Endpoints and definitions	Primary endpoint	% subjects with ME	The proportion of subjects who developed macular oedema (ME) within 90 days following cataract surgery.
	Secondary endpoint	% subjects with BCVA improvement of ⩾ 15 at D14-D90	The proportion of subjects with improvements in BCVA of ≥ 15 letters from the preoperative baseline to Day 14 and maintained through Day 90 (primary endpoint in the US efficacy) analysis plan
Database lock	13 May 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set, 90 days after cataract surgery		
Descriptive statistics and estimate variability	Treatment group	Nevanac	Vehicle
	Number of subject	298	300
	% subjects with ME	2.3	17.3
	SE	0.9	2.2
	% subjects with BCVA improvement of ⩾ 15	61.7	43.0
	SE	2.8	2.9

Effect estimate per comparison	Primary endpoint % subjects with ME	Comparison groups	Nevanac vs vehicle
		Mean difference	-14,9
		95% CI	(-21.6, - 9.3)
		P-value	<0.001
	Secondary endpoint % subjects with BCVA improvement of ⩾ 15	Comparison groups	Nevanac vs vehicle
		Mean difference	18.7
		95% CI	(8.9- 28.3)
		P-value	<0.001

Table 20 Summary of Efficacy for trial C-12-071

Title: Randomized, Double-Masked, Vehicle Controlled, Clinical Evaluation to Assess the Safety and Efficacy of Nepafenac Ophthalmic Suspension, 0.3% for Improvement in Clinical Outcomes Among Diabetic Subjects Following Cataract Surgery (conducted in United States, Europe, Middle East, and Africa, Latin America and the Caribbean, and the Asia Pacific region).			
Study identifier	C-12-071		
Design	Randomised, double-blind, vehicle-controlled.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		90 days not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Nepafenac 3mg/ml		1 drop once daily for 90 days, 301 patients randomised
	Vehicle		1 drop once daily for 90 days, 304 patients randomised
Endpoints and definitions	Primary endpoint	% subjects with ME	The proportion of subjects who developed macular oedema (ME) within 90 days following cataract surgery.
	Secondary endpoint	% subjects with BCVA improvement of ⩾ 15 at D14-D90	The proportion of subjects with improvements in BCVA of ≥ 15 letters from the preoperative baseline to Day 14 and maintained through Day 90 (primary endpoint in the US efficacy) analysis plan
Database lock	28 May 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set, 90 days after cataract surgery		
Descriptive statistics and estimate variability	Treatment group	Nepafenac	Vehicle
	Number of subject (FAS)	289	293
	% subjects with ME	5.9	14.3
	SE	1.4	2
	% subjects with BCVA improvement of ⩾ 15	48.8	50.5
	SE	2.9	2.9
Effect estimate per comparison	Primary endpoint % subjects with ME	Comparison groups	Nevanac vs vehicle
		Mean difference	-6.8
		95% CI	(-14.2, -0,8)
		P-value	0.001
	Secondary endpoint % subjects with BCVA	Comparison groups	Nevanac vs vehicle
		Mean difference	-1.8
		95% CI	(-12.6, 9.2)

	improvement of ⩾ 15	P-value	0.671

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis of study C-12-067 and C-12-071

A pooled analysis showed that a lower proportion of subjects in the Nepafenac 3 mg/mL group (4.1%) developed ME within 90 days following surgery compared to vehicle group (15.9%; p < 0.001).

It was also shown that a higher proportion of subjects in the Nepafenac 3 mg/ mL group (55.4%) achieved clinically relevant improvement of ≥ 15 letters from Preoperative Baseline to Day 14 and maintained through Day 90 compared to vehicle group (46.7%, p = 0.003).

Visual outcomes

The MAH has conducted several analyses to demonstrate correlation between the treatment and its effect on visual acuity. Additional analysis exploring the relation between ME and Visual Function were also performed.

In both studies, subjects who developed ME had substantially lower odds (80% lower in C-12-067 and 50% lower in C-12-071) of achieving sustained gains in BCVA (≥ 15 letters from pre-operative baseline to Day 14 maintained through Day 90) compared to subjects who did not develop ME (OR=0.2, p< 0.001 in C-12-067 and OR=0.5, p = 0.011 in C-12-071).

Subjects who developed ME also had substantially higher odds of losing >5 letters (over 4-fold higher in C-12-067 and 3-fold higher in C-12-071, p<0.001 for both) and >10 letters (over 3-fold higher in C-12-067, p<0.001 and 2.5-fold higher in C-12-071, p=0.011) from postoperative Day 7. These declines in BCVA were observed despite subjects having been promptly started with rescue treatment once they developed ME (ME was defined as 30% or more increase in macular thickness), in some cases with multiple medications including intravitreal injections with VEGF inhibitors.

Efficacy at 60 days post- surgery

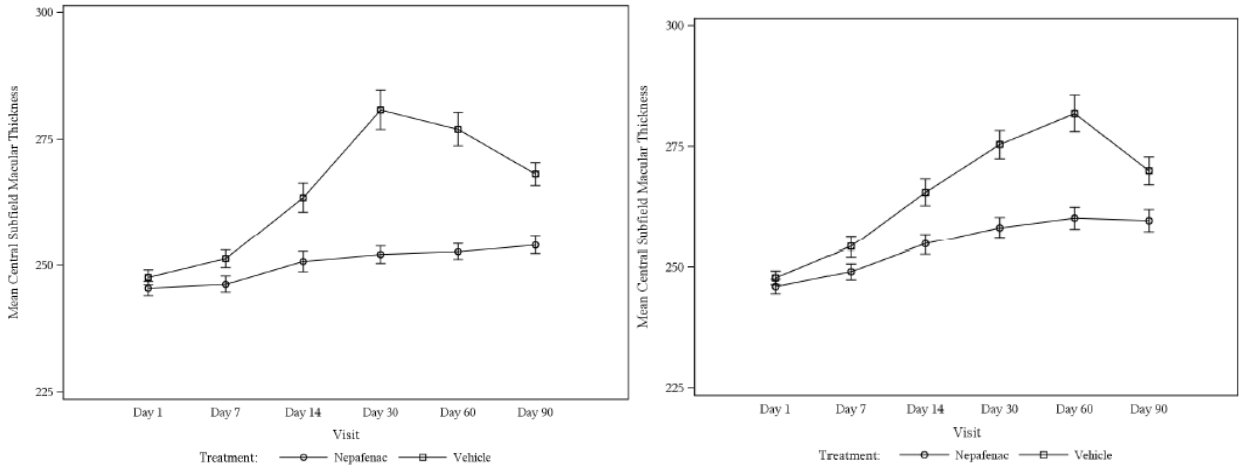
Nevanac 1 mg/ml posology was approved based on additional analyses, which showed that there was no additional benefit beyond 60 days of treatment. Similar analyses were also performed for Nevanac 3mg/ml. The responder rates (percentage of patients who develop macular oedema after surgery) are summarised in table 21 and summary of anatomical parameters (mean central subfield macular thickness by visit) presented in Figure 3.

Table 21 Percentage of subjects who develop macular oedema by Day 60 and Day 90 in Phase III trials (C-12-067 and C-12-071)

	C-12-067		C-12-071	
	Nepafenac (N=298)	**Vehicle (N=300)**	**Nepafenac (N=289)**	**Vehicle (N=293)**
Day 60 N (%)	6 (2.0)	51 (17.0)	13 (4.5)	40 (13.7)
Difference (95% CI)	-15.1 (-21.8, -9.6)		-7.6 (-14.9, -2.0)	
p-value	< 0.001		< 0.001	
Day 90 N (%)	7 (2.3)	52 (17.3)	17 (5.9)	42 (14.3)
Difference (95% CI)	-14.9 (-21.6, -9.3)		-6.8 (-14.2, -0.8)	
p-value	< 0.001		< 0.001	

Figure 3 Mean Central Subfield Macular Thickness by Visit

Study 067 **Study 071**



Supportive studies

Studies C-07-43 and C-09-003 were conducted with Nepafenac 1 mg/mL and were similar in design to the Nepafenac 3 mg/mL studies.

C-07-43 study enrolled 263 subjects (133 in Nepafenac 1 mg/mL group and 130 in Vehicle group), of which 251 subjects (125 in Nepafenac 1 mg/mL group and 126 in Vehicle group) were included in the FAS. Study C-09-003 was terminated early due to recruitment issues. 175 subjects were enrolled at the time of termination (87 in Nepafenac 1 mg/mL group and 88 in Vehicle group) of which 160 subjects (80 in Nepafenac 1 mg/mL group and 80 in Vehicle group) were included in the FAS. Both studies C-07-43 and C-09-003 have been reanalysed on the basis of the endpoints and analytical strategies employed in studies C-12-067 and C-12-071.

Primary and Secondary Efficacy Results in the full analysis set (FAS)

- Development of macular oedema (Primary endpoint):

C-07-43: Nepafenac 1 mg/mL significantly reduced the risk of macular oedema development within 90 days following cataract surgery. A significantly lower proportion of subjects in Nepafenac 1 mg/mL group (3.2%) developed ME (defined as ≥ 30% increase from preoperative baseline in central subfield macular thickness) within 90 days following surgery than subjects in the Vehicle group (16.7%; p < 0.001).

C-09-003: Nepafenac 1 mg/mL significantly reduced the risk of macular oedema development within 90 days following cataract surgery. A significantly lower proportion of subjects in Nepafenac 1 mg/mL group (5.0%) developed ME (defined as ≥ 30% increase from preoperative baseline in central subfield macular thickness) within 90 days following surgery than subjects in the Vehicle group (17.5%; p = 0.018).

Although the definition of ME was the same, this endpoint was not pooled since the OCT used was different between the 2 studies– TD-OCT was used in C-07-43 and SD-OCT in C-09-003.

- BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and Maintained through Day 90 (first secondary endpoint):

C-07-43: A higher proportion of subjects achieved improvement of ≥ 15 Letters from pre-operative baseline to Day 14 and maintained through Day 90 in the Nepafenac 1 mg/mL group (38.4%) compared to the Vehicle group (21.4%, p = 0.003).

C-09-003: A higher proportion of subjects achieved improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and maintained through Day 90 in the Nepafenac 1 mg/mL group (35.0%) compared to the Vehicle group (25.0%, p = 0.172).

Pooled: A higher proportion of subjects achieved improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and maintained through Day 90 in the Nepafenac 1 mg/mL group (37.1%) compared to the Vehicle group (22.8%, p = 0.003).

Table 22 Summary of Primary and Secondary Endpoints (FAS)

Endpoint	Nepafenac Percentage (SE)	Vehicle Percentage (SE)	Odds Ratio (95% CI)	P-value
C-07-43				
Development of Macular Edema [a]	3.2 (1.6)	16.7 (3.3)	0.2 (0.1, 0.5)	0.001
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and Maintained through Day 90 [b]	38.4 (4.4)	21.4 (3.7)	2.4 (1.4, 4.2)	0.003
BCVA > 5 Letter Loss from Day 7 to Any Visit [b]	15.2 (3.2)	42.9 (4.4)	0.2 (0.1, 0.4)	<0.001
BCVA > 10 Letter Loss from Day 7 to Any Visit [b]	7.2 (2.3)	28.6 (4.0)	0.2 (0.1, 0.4)	<0.001
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 90 [b]	55.2 (4.4)	34.9 (4.2)	2.4 (1.4, 3.9)	0.001
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 60 [b]	52.0 (4.5)	39.7 (4.4)	1.7 (1.0, 2.8)	0.046
C-09-003				
Development of Macular Edema [a]	5.0 (2.4)	17.5 (4.2)	0.2 (0.1, 0.8)	0.018
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and Maintained through Day 90 [b]	35.0 (5.3)	25.0 (4.8)	1.6 (0.8, 3.2)	0.172
BCVA > 5 Letter Loss from Day 7 to Any Visit [b]	45.0 (5.6)	53.8 (5.6)	0.7 (0.4, 1.3)	0.274
BCVA > 10 Letter Loss from Day 7 to Any Visit [b]	37.5 (5.4)	46.3 (5.6)	0.7 (0.4, 1.3)	0.269
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 90 [b]	47.5 (5.6)	35.0 (5.3)	1.7 (0.9, 3.2)	0.111
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 60 [b]	52.5 (5.6)	43.8 (5.5)	1.4 (0.8, 2.6)	0.272
Pooled				
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 14 and Maintained through Day 90 [b]	37.1 (3.4)	22.8 (2.9)	2.0 (1.3, 3.1)	0.001
BCVA > 5 Letter Loss from Day 7 to Any Visit [b]	26.8 (3.1)	47.1 (3.5)	0.4 (0.3, 0.6)	<0.001
BCVA > 10 Letter Loss from Day 7 to Any Visit [b]	19.0 (2.7)	35.4 (3.3)	0.4 (0.3, 0.7)	<0.001
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 90 [b]	52.2 (3.5)	35.0 (3.3)	2.0 (1.4, 3.0)	<0.001
BCVA Improvement of ≥ 15 Letters from Preoperative Baseline to Day 60 [b]	52.2 (3.5)	41.3 (3.4)	1.6 (1.1, 2.3)	0.025

Nepafenac = Nepafenac Ophthalmic Suspension, 0.1%
Vehicle = Nepafenac Ophthalmic Suspension Vehicle
SE = Standard error, CI = Confidence interval
[a] Primary endpoint
[b] Secondary endpoint
Hypotheses are tested in the order of primary endpoint followed by secondary endpoint in the order listed.
Each hypothesis will be relevant only if the preceding hypotheses have been rejected at the 5 level of significance.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Two randomised, double-masked, vehicle-controlled trials (Study C-12-067 and Study C-12-071) formed the main basis to support the efficacy of Nevanac 3mg/ml in the proposed indication.

Both studies recruited Type 1 or 2 diabetic patients with non proliferative retinopathy and decreased visual acuity (BCVA of 73 letters or worse) at screening. This population can be considered to be at risk of developing macular oedema as a consequence of cataract surgery since a 4-fold increase in incidence of postoperative oedema has been described in patients with diabetes in comparison to subjects who did not have diabetes at the time of the surgery (Chu, 2016). The study population was furthermore considered representative of the target population in line with the proposed indication.

Exclusion criteria aimed at ruling out patients with ME present at the time of surgery, ocular conditions that could increase the risk of development of pseudophakic ME or complications from topical NSAIDs. Concomitant use of topical and systemic anti-inflammatory treatment as well as topical prostaglandins (associated with an increased risk of CME) prior to enrolment were not allowed. The study exclusion criteria were considered appropriate.

The nepafenac dose selected in this study (1 eye drop nepafenac 3mg/ml instilled into the study eye once daily) was in accordance with that already approved for prevention of pain and inflammation after cataract surgery. With respect to the duration of treatment, the MAH has chosen a 90 day study duration based on the time period in which ME usually occurs.

The evaluation of efficacy mainly relied on the presence of ME as measured by anatomic parameters. Spectral-domain optical coherence tomography (OCT) is a non-contact, micron-level, diagnostic system that uses infrared light to provide high resolution images of the retina and retinal thickness. Two different brands of SD-OCT equipment were used to measure the macular thickness and volume and in consequence differences in measures could be potentially expected. In principle, it should not impact on parameters expressed as relative changes (e.g the primary efficacy variable) but it might do it on those variables defined as absolute changes (e.g mean thickness of retina). The MAH has provided further clarification regarding the risk of using two different SD-OCT equipments on the final outcome

a) a single brand of SD-OCT was selected by each centre
b) harmonization was carried out by the central reading centre
c) the anatomic variables (those expressed as percentage of change and the measurements based upon macular volume) were relative to baseline
d) although the frequency of use of the OCT equipments was different between the two studies, the distribution of equipments between treatment groups was balanced.

Taking the above into consideration, the CHMP agreed that no relevant impact on the overall results would be expected.

Overall, more than 1200 patients were randomised in the two pivotal trials. The treatment groups were well balanced with respect to demographic and disease-related baseline characteristics. Most of the recruited patients presented with moderate retinopathy severity. Mean age of patients was around 67 years ranging from 30 to 94 years old, which represents the broad spectrum of the target population. A high proportion of elderly patients (66.5%) were included.

All patients in the studies were treated with prednisolone eye drops for 4 weeks post-surgery. Although a synergistic effect of NSAIDs and corticosteroid has been suggested in literature (Kim, 2015), doubts regarding the benefit of additional use have also been raised (Kim. 2016). Without a control group not receiving corticosteroids a definitive conclusion regarding the role of each component of the association cannot be undoubtedly reached.

Efficacy data and additional analyses

Both main studies showed a statistically significant effect of nepafenac with regards to the primary endpoint. Significantly fewer subjects receiving Nepafenac 3 mg/ml OD (2.3% in Study 067 and 5.9% in Study 071) developed ME 12 weeks after surgery in comparison to patients receiving Vehicle (17.3% and 14.3%, respectively). The macular thickness was substantially less in patients treated with Nepafenac than in patients treated with Vehicle at the end of treatment period (254.1 microns vs 268.2 microns [$p < 0.001$], in the Study 067; 259.7 microns vs 270.0 microns [$p= 0.003$] , in the Study 071) , and the mean maximum change from baseline in central subfield macular thickness in Nepafenac group was lower than the observed change in patients treated with Vehicle (2.7% versus 13.2 %, respectively in Study 067 [$p < 0.001$]; and 5.4% versus 13.1%, respectively in Study 071, [$p< 0.001$]).

Only Study 067 reached the expected 13% difference between active and vehicle arms in the development of ME according to the predefined criteria. The difference observed in Study 071 (6.8%), although

statistically significant, was of questionable clinical relevance. The MAH attributed the difference between studies to the better than expected behaviour of the Vehicle arm (incidence of 14.3% of macular oedema, which was inferior to the rates reported in the other nepafenac studies in this indication) rather than a smaller effect in the nepafenac arm. This was acknowledged by the CHMP. Analysis of demographical or disease related characteristics between studies did not provide additional reasons to explain the observed differences between studies.

Given that ME may have an impact on visual function, it was important to establish if the observed treatment effect on ME translated into a benefit on visual function, measured as visual acuity. Only Study 067 showed a significant difference between groups in the percentage of patients with an increase in BCVA of more than 15 letters (18.7%; p<0.001). In Study 071 the difference between Nepafenac and Vehicle groups was -1.8% (p=0.671). Some positive trend was nevertheless observed in some BCVA endpoints in this study.

The MAH submitted several additional analyses regarding the effect of nepafenac on visual acuity. A lack of clear effect on vision observed in Study 071 has been attributed by the MAH to a better performance of Vehicle arm, which was acknowledged by the CHMP. Consistency between the explored visual outcome variables was shown. When the benefit on vision was expressed in terms of responder rates (e.g. BCVA improvement of ≥ 15 letters, worsening of > 5 letters) Nevanac 3 mg/ml showed better responses than Vehicle in Study 067. Generally, a higher percentage of patients treated with Nepafenac 3 mg/ml (55.7% in Study 067 and 40.8% in Study 071) than those treated with Vehicle (44.3% and 32.4%, respectively) attained a 20/20 or better vision at the end of the study.

A post-hoc analysis has been conducted in order to establish the correlation between the prevention of ME and the vision outcomes. Patients developing ME, regardless of the treatment received, achieved poorer results (lower rate of patients with ≥ 15 letters improvement [22.0% in Study 067, 33.9% in Study 071] and higher rate of patients with > 5 letters worsening [50.8% and 35.6%, respectively]) than those patients without ME (improvement of ≥ 15 letters 55.5% and 51.4% [in Study 067 and Study 071, respectively] and worsening of > 5 letters 18.2% and 15.7% [in Study 067 and Study 071, respectively].

Two additional studies have been submitted: Study C-07-43 and C-09-003. These studies were previously conducted with Nepafenac 1 mg/mL in order to support the same indication for the lower strength. The study data were reanalysed in line with the endpoint definitions in studies 067 and 071. The observed response both in terms of prevention of ME and visual acuity outcomes was broadly in line with that observed in Study 067. Given that the daily dose would be the same for Nevenac 1mg/ml TID and Nevenac 3mg/ml QD, the results of these earlier studies were considered supportive for efficacy demonstration.

Although the trials' duration was 90 days, the proposed posology for the 3 mg/ml strength was 60 days which is identical to recommended treatment duration for the 1 mg/ml strength. The 1 mg/ml strength posology has previously been approved based on additional analyses, which showed that there was no additional benefit beyond 60 days of treatment. Similar analyses performed for Nevanac 3mg/ml have also shown that little benefit appears to be added when the treatment is extended from 60 to 90 days. As a consequence, a 60 day treatment duration has been recommended in the SmPC.

2.4.3. Conclusions on the clinical efficacy

Based on the data presented in support of this application, the CHMP was of the view that the efficacy of Nevanac 3mg/ml in the prevention of post-operative oedema in diabetic patients has been demonstrated. Although the effect observed in one of the 2 pivotal studies was lower than expected, the additional analyses conducted by the MAH and supportive studies conducted with Nevanac 1mg/ml provide further reassurance on the efficacy of Nevanac 3mg/ml in the proposed indication.

2.5. Clinical safety

Introduction

The safety evaluation was based on:

- An analysis of the pooled safety data from studies C-12-067 and C-12-071 (Main analysis)
- A historical comparison between Nepafenac 3 mg/ml and Nepafenac 1 mg/ml eye drops, suspension, based on pooled data from 2 Nepafenac 1 mg/ml post-cataract macular oedema clinical trials (C-07-43 and C-09-003).

The safety assessment included the extent of exposure to study drug, adverse events and other safety-related parameters; slit-lamp parameters (inflammatory cells, aqueous flare, corneal oedema, bulbar redness, and corneal epithelium integrity (fluorescein staining)), intraocular pressure and dilated fundus parameters (peripheral retina/macula/choroid, and optic nerve).

Patient exposure

The development program consisted of 2 clinical studies (C-12-067 and C-12-071) including a total of 1191 subjects in the safety analysis set (594 subjects exposed to Nepafenac 3 mg/ml).

The previously conducted clinical trials (C-07-43 and C-09-003) of Nepafenac 1 mg/ml dosed TID in the same indication included a total of 419 subjects (209 subjects exposed to Nepafenac 1 mg/ml).

Table 23 Overview of exposure to study drug - Post Cataract ME studies

			Nepafenac 3 mg/mL QD	Nepafenac 1mg/Ml TID	Nepafenac Vehicle 3 mg/mL QD	Nepafenac Vehicle 1mg/Ml TID
			(N = 594)	(N = 209)	(N = 597)	(N = 210)
Post-Cataract Macular Edema Studies	**Protocol Number**	**Safety N**	**QD**	**TID**	**QD**	**TID**
	C-12-067	603	301		302	
	C-12-071	588	293		295	
	C-07-43	253		126		127
	C-09-003	166		83		83
	Subtotal	**1610**	**594**	**209**	**597**	**210**

Nepafenac 3 mg/mL = Nepafenac 3 mg/mL eye drops, suspension
Nepafenac 1 mg/mL = Nepafenac 1 mg/mL eye drops, suspension
Nepafenac Vehicle 3 mg/mL = Nepafenac 3 mg/mL eye drops, suspension vehicle
Nepafenac Vehicle 1 mg/mL = Nepafenac1mg/mL eye drops, suspension vehicle

The great majority of subjects were exposed for more than 60 days. The median exposure was 90 days or greater for Nepafenac 3 mg/mL and Nepafenac 1 mg/mL groups (see Table 24 below).

Table 24 Exposure to Investigational Product in Post cataract ME studies

	Nepafenac 0.3% (QD) (N = 594)	Nepafenac 0.1% (TID) (N = 209)	Nepafenac overall (N = 803)	Vehicle 0.3% (QD) (N = 597)	Vehicle 0.1% (TID) (N = 210)	Vehicle overall (N = 807)
Exposure (in days)						
n	594	209	803	597	210	807
Mean (SD)	86.8 (16.6)	84.8 (21.2)	86.3 (17.9)	80.2 (22.9)	77.8 (25.6)	79.5 (23.7)
Median	90.0	92.0	91.0	88.0	88.0	88.0
(Min, Max)	(1, 174)	(2, 117)	(1, 174)	(1, 124)	(1, 109)	(1, 124)
Exposure Categories, n (%)						
1-14 days	14 (2.4)	5 (2.4)	19 (2.4)	16 (2.7)	6 (2.9)	22 (2.7)
15-30 days	5 (0.8)	8 (3.8)	13 (1.6)	31 (5.2)	14 (6.7)	45 (5.6)
31-60 days	10 (1.7)	5 (2.4)	15 (1.9)	46 (7.7)	22 (10.5)	68 (8.4)
61-90 days	271 (45.6)	74 (35.4)	345 (43.0)	272 (45.6)	87 (41.4)	359 (44.5)
> 90 days	294 (49.5)	117 (56.0)	411 (51.2)	232 (38.9)	81 (38.6)	313 (38.8)

Baseline characteristics

Regarding demographic baseline characteristics see section 2.4.

Adverse events

Adverse events (AEs) were obtained as solicited comments from study subjects and as observations by each study Investigator.

AEs were defined as any untoward change (expected or unexpected) in a patient's ophthalmic and/or medical health in the clinical trials that were assessed as clinically relevant by the Investigator. In studies C-12-067 and C-12-071 AEs were also collected on a pre-treatment basis (from the time of consent up to the first exposure to the study medication) and a post-treatment basis (after subjects permanently discontinued the study medication until the time they exited from the trials).

The assessment of AEs and their relationship to the study drug were performed by the Investigators according to their clinical judgement.

Common adverse events

The commonly reported AEs (≥ 1% in either Nepafenac 3 mg/mL group or in Nepafenac 1 mg/ml group) are listed in Table 30. The analysis of AEs was mainly focused on treatment emergent adverse events (TEAE) i.e. the AEs occurred from the time of first exposure to the study medication up to the time the study medication was permanently discontinued.

Table 25 Common Treatment Emergent Adverse Events

Coded Adverse Event	Nepafenac 3 mg/mL QD (N = 594) N (%)	Nepafenac 1 mg/mL TID (N = 209) N (%)	Nepafenac Vehicle 3 mg/mL QD (N =597) N (%)	Nepafenac Vehicle 1 mg/mL TID (N = 210) N (%)
Cardiac disorders				
Coronary artery disease	1 (0.2)	3 (1.4)	1 (0.2)	0 (0.0)
Eye disorders				
Anterior chamber cell	1 (0.2)	4 (1.9)	4 (0.7)	0 (0.0)
Anterior chamber flare	0 (0.0)	2 (1.0)	1 (0.2)	1 (0.5)
Blepharitis	3 (0.5)	2 (1.0)	3 (0.5)	1 (0.5)
Conjunctival haemorrhage	3 (0.5)	2 (1.0)	9 (1.5)	1 (0.5)
Corneal epithelium defect	3 (0.5)	3 (1.4)	3 (0.5)	2 (1.0)
Corneal erosion	1 (0.2)	2 (1.0)	0 (0.0)	0 (0.0)
Corneal oedema	6 (1.0)	6 (2.9)	14 (2.3)	9 (4.3)
Dry eye	11 (1.9)	5 (2.4)	21 (3.5)	3 (1.4)
Eye pain	6 (1.0)	1 (0.5)	18 (3.0)	4 (1.9)
Foreign body sensation in eyes	7 (1.2)	0 (0.0)	10 (1.7)	1 (0.5)
Macular oedema	4 (0.7)	2 (1.0)	15 (2.5)	3 (1.4)
Ocular hypertension	6 (1.0)	0 (0.0)	3 (0.5)	0 (0.0)
Punctate keratitis	13 (2.2)	9 (4.3)	13 (2.2)	9 (4.3)
Visual acuity reduced	6 (1.0)	3 (1.4)	5 (0.8)	1 (0.5)
Vitreous haemorrhage	3 (0.5)	2 (1.0)	1 (0.2)	0 (0.0)
Gastrointestinal disorders				
Diarrhoea	2 (0.3)	2 (1.0)	4 (0.7)	0 (0.0)
Nausea	5 (0.8)	2 (1.0)	1 (0.2)	1 (0.5)
Vomiting	1 (0.2)	2 (1.0)	1 (0.2)	0 (0.0)
Infections and infestations				
Nasopharyngitis	7 (1.2)	0 (0.0)	11 (1.8)	0 (0.0)
Injury, poisoning and procedural complications				
Injury	0 (0.0)	6 (2.9)	0 (0.0)	4 (1.9)
Investigations				
Blood pressure increased	0 (0.0)	2 (1.0)	2 (0.3)	1 (0.5)
Intraocular pressure increased	23 (3.9)	5 (2.4)	24 (4.0)	4 (1.9)
Metabolism and nutrition disorders				
Hypercholesterolaemia	0 (0.0)	2 (1.0)	2 (0.3)	0 (0.0)
Nervous system disorders				
Headache	7 (1.2)	1 (0.5)	14 (2.3)	2 (1.0)
Vascular disorders				
Hypertension	3 (0.5)	4 (1.9)	4 (0.7)	5 (2.4)

Common AEs = All treatment-emergent AEs (related and unrelated, combined) occurring at an incidence of ≥ 1% in the Nepafenac 3 mg/mL treatment group or in the Nepafenac 1 mg/mL (TID) treatment group.
Adverse events are coded using MedDRA version 16.0
Source: Tables 5 and 6 in Section 53532.

Ocular TEAEs

The summary of ocular TEAEs is presented in the Table below.

Table 26 Summary of Ocular Treatment Emergent Adverse Events

	Nepafenac 0.3% (QD) (N = 594)				Nepafenac 0.1% (TID) (N = 209)				Nepafenac overall (N = 803)				Vehicle 0.3% (QD) (N = 597)				Vehicle 0.1% (TID) (N = 210)				Vehicle overall (N = 807)			
	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR
Ocular event																								
Any TEAE	142	(23.9)	210	32.21	40	(19.1)	71	25.76	182	(22.7)	281	30.53	183	(30.7)	286	44.24	53	(25.2)	91	38.63	236	(29.2)	377	42.84
TEAE related to IP	14	(2.4)	15	2.62	8	(3.8)	9	4.53	22	(2.7)	24	3.09	15	(2.5)	17	2.76	7	(3.3)	9	4.28	22	(2.7)	26	3.11
Any serious TEAE	3	(0.5)	3	0.56	0	(0.0)	0	0	3	(0.4)	3	0.42	2	(0.3)	5	0.36	1	(0.5)	1	0.60	3	(0.4)	6	0.42
Serious TEAE related to IP	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
AE leading to discontinuation	1	(0.2)	1	0.18	3	(1.4)	3	1.67	4	(0.5)	4	0.55	1	(0.2)	1	0.18	7	(3.3)	7	4.24	8	(1.0)	8	1.11
Study eye event																								
Any TEAE	125	(21.0)	171	27.76	36	(17.2)	62	22.99	161	(20.0)	233	26.53	174	(29.1)	249	41.27	48	(22.9)	80	34.55	222	(27.5)	329	39.60
TEAE related to IP	14	(2.4)	15	2.62	7	(3.3)	8	3.96	21	(2.6)	23	2.95	15	(2.5)	17	2.76	7	(3.3)	8	4.28	22	(2.7)	25	3.11
Any serious TEAE	3	(0.5)	3	0.56	0	(0.0)	0	0	3	(0.4)	3	0.42	1	(0.2)	1	0.18	1	(0.5)	1	0.60	2	(0.2)	2	0.28
Serious TEAE related to IP	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
AE leading to discontinuation	1	(0.2)	1	0.18	2	(1.0)	2	1.11	3	(0.4)	3	0.41	1	(0.2)	1	0.18	7	(3.3)	7	4.24	8	(1.0)	8	1.11
Nonstudy eye event																								
Any TEAE	33	(5.6)	39	6.29	8	(3.8)	9	4.51	41	(5.1)	48	5.84	30	(5.0)	37	5.65	9	(4.3)	11	5.55	39	(4.8)	48	5.62
TEAE related to IP	0	(0.0)	0	0	1	(0.5)	1	0.56	1	(0.1)	1	0.14	0	(0.0)	0	0	1	(0.5)	1	0.60	1	(0.1)	1	0.14
Any serious TEAE	0	(0.0)	0	0	0	(0.0)	0	0	0	(0.0)	0	0	2	(0.3)	4	0.36	0	(0.0)	0	0	2	(0.2)	4	0.28
Serious TEAE related to IP	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
AE leading to discontinuation	0	(0.0)	0	0	1	(0.5)	1	0.56	1	(0.1)	1	0.14	0	(0.0)	0	0	0	(0.0)	0	0	0	(0.0)	0	0

N = Total number of subjects in each treatment group; n = Number of subjects with the events; E = Number of events; IP = Investigational product.
If a subject has multiple occurrences of an AE, the subject is presented only once in the respective subject count column (n) for the corresponding AE.
Events are counted each time in the event (E) column. Adverse events are coded using MedDRA version 16.0.
EAIR = Exposure adjusted incidence rate
EAIR = Number of subjects with a specific event divided by total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the event multiplied by 10,000.

Non ocular TEAE

The overview of non ocular TEAEs is presented in the Table below.

Table 27 Summary of Nonocular Treatment Emergent Adverse Events

	Nepafenac 0.3% (QD) (N = 594)				Nepafenac 0.1% (TID) (N = 209)				Nepafenac overall (N = 803)				Vehicle 0.3% (QD) (N = 597)				Vehicle 0.1% (TID) (N = 210)				Vehicle overall (N = 807)			
	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR	n	%	E	EAIR
Any TEAE	**104**	**(17.5)**	**162**	**21.60**	**38**	**(18.2)**	**58**	**23.69**	**142**	**(17.7)**	**220**	**22.12**	**124**	**(20.8)**	**240**	**26.06**	**36**	**(17.1)**	**56**	**24.22**	**160**	**(19.8)**	**296**	**25.62**
TEAE related to IP	1	(0.2)	1	0.18	1	(0.5)	1	0.56	2	(0.2)	2	0.28	0	(0.0)	0	0	0	(0.0)	0	0	0	(0.0)	0	0
Any serious TEAE	**24**	**(4.0)**	**35**	**4.52**	**10**	**(4.8)**	**14**	**5.73**	**34**	**(4.2)**	**49**	**4.82**	**26**	**(4.4)**	**35**	**4.81**	**9**	**(4.3)**	**10**	**5.53**	**35**	**(4.3)**	**45**	**4.98**
Serious TEAE related to IP	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0	0	(0)	0	0
AE leading to discontinuation	**0**	**(0.0)**	**0**	**0**	**3**	**(1.4)**	**3**	**1.67**	**3**	**(0.4)**	**3**	**0.42**	**4**	**(0.7)**	**10**	**0.72**	**3**	**(1.4)**	**3**	**1.81**	**7**	**(0.9)**	**13**	**0.97**

N = Total number of subjects in each treatment group; n = Number of subjects with the events; E = Number of events; IP = Investigational product
If a subject has multiple occurrences of an AE, the subject is presented only once in the respective subject count column (n) for the corresponding AE.
Events are counted each time in the event (E) column. Adverse events are coded using MedDRA version 16.0.
EAIR = Exposure adjusted incidence rate
EAIR = Number of subjects with a specific event divided by total exposure-time among the subjects in the treatment group and at risk of an initial occurrence of the event multiplied by 10,000.

In general, the majority of TEAEs reported in post-cataract ME studies (C12-067, C-12-071, C-07-43, C-09-003) were local and related to eye disorders. Among the AEs reported (related and unrelated to treatment), corneal oedema, dry eye, eye pain, foreign body sensation in eyes, ocular hypertension, punctate keratitis, intraocular pressure increased and visual acuity reduced were the most commonly

observed AEs in the Nepafenac 3 mg/ml group with an incidence ≥ 1%. Overall, the rate of ocular TEAEs was slightly higher in the Vehicle group, with the exception of corneal erosion, ocular hypertension and vitreous haemorrhage that appeared with a higher incidence in the Nepafenac 3 mg/ml group.

Treatment-related adverse events (adverse drug reactions; ADRs)

The adverse reactions related to the treatment are listed in the Table below.

Table 28 Overall frequency and incidence of ADRs in Post cataract ME studies

Coded Adverse Event	Nepafenac 3 mg/mL QD (N = 594) N (%)	Nepafenac 1 mg/mL TID (N = 209) N (%)	Nepafenac Vehicle 3 mg/mL QD (N =597) N (%)	Nepafenac Vehicle 1 mg/mL TID (N = 210) N (%)
Treatment-Emergent (ADRs)				
Eye disorders				
Corneal disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Corneal epithelium defect	0 (0.0)	1 (0.5)	1 (0.2)	0 (0.0)
Corneal erosion	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Corneal irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Corneal oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Dellen	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Dry eye	1 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)
Eye irritation	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)
Eye pain	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Eye pruritus	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Foreign body sensation in eyes	2 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)
Keratitis	2 (0.3)	0 (0.0)	2 (0.3)	0 (0.0)
Keratopathy	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Punctate keratitis	4 (0.7)	6 (2.9)	6 (1.0)	4 (1.9)
Investigations				
Vital dye staining cornea present	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders				
Headache	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders				
Dermatitis allergic	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

The most commonly reported ADRs in the Nepafenac 3 mg/ml group were punctate keratitis (0.7% in Nepafenac 3 mg/ml, 1% in vehicle, 2.9% in Nepafenac 1 mg/ml), keratitis (0.3%, 0.3%, 0.0%) and foreign body sensation in eyes (0.3%, 0.5%, 0.0%). Dry eye was identified as a new ADR with a rare frequency.

Serious adverse event / deaths / other significant events

- **Serious adverse event (SAE)**

No treatment-related SAEs were reported.

Nepafenac 3 mg/ml (QD) studies

Among the 27 (4.5%) subjects who experienced treatment emergent serious adverse events in the Nevenac 3mg/ml treatment group, ocular SAEs were reported for 3 (0.5%) subjects (posterior capsule rupture, device dislocation, and eye injury). A total of 24 (4.0%) subjects reported non-ocular SAEs.

Among the 28 (4.7%) subjects who experienced treatment emergent serious adverse events in Nevanac 3mg/ml vehicle treatment group, 2 (0.3%) subjects experienced ocular SAEs (VIth nerve paralysis and intraocular injection) and 26 (4.4%) subject experienced nonocular SAEs.

Nepafenac 1 mg/ml (TID) studies

Overall, 10 (4.8%) subjects experienced treatment emergent serious adverse events in the Nepafenac 1 mg/mL treatment group. All of these SAEs were nonocular.

Among the 10 (4.8%) subjects in the Nepafenac 1 mg/ml Vehicle treatment group who experienced treatment emergent serious adverse events, 1 (0.5%) subject experienced 1 ocular SAE (posterior capsule rupture) and 9 (4.3%) subjects experienced nonocular SAEs.

- **Deaths**

In Studies C-12-067 and C12-071, 1 subject in the Vehicle group died; additionally, 1 subject in the Nepafenac group and 4 subjects in the Vehicle group died. One subject who was never exposed to study medication died.

None of these events were considered by the Investigator to be treatment-related.

No deaths were reported in the C-07-43 study. One death was reported in the C-09-003 study for a subject treated with Nepafenac 1 mg/ml. This subject died after discontinuing from the study and the death was not considered by the Investigator to be treatment-related.

Laboratory findings

- **Clinical Laboratory Evaluation**

Clinical laboratory evaluations were not conducted during the clinical studies.

- **Vital Signs, Physical Findings, and Other Observations Related to Safety**

During studies C-12-067 and C-12-071 the following parameters were measured:

- Intraocular pressure
- Slit-Lamp Examination: aqueous cells, aqueous flare, corneal oedema, bulbar redness and corneal epithelium integrity (fluorescein staining).
- Dilated Fundus Exam: peripheral, retina/macula/choroid, optic nerve.

Intraocular pressure (IOP)

Intraocular pressure (IOP) was assessed in the study eye for all subjects. The maximum change in IOP for each subject was calculated as the maximum absolute change in IOP between baseline and all study visits, either scheduled or unscheduled.

Mean IOP was higher at Visit 2 (the first day after cataract surgery) compared to any other visit for both treatment groups. This increase in mean IOP at Visit 2 is not unexpected immediately after cataract surgery and was transient as shown by mean IOPs at all post-operative visits. A similar trend was also observed in the Vehicle treatment group. A review of the range of IOP changes revealed that most subjects in both treatment groups experienced maximum changes in IOP of no more than 10 mmHg.

No ADRs were reported for changes in IOP among subjects in both treatment groups.

Slit-Lamp Examination

A shift in aqueous cell scores from normal at baseline to abnormal at Day 1 was noted for 19 subjects in the Nepafenac group and 23 subjects in the Vehicle group. 1 subject in each group had a shift in aqueous cell scores from normal at baseline to abnormal at Day 7. No such a shift was observed at any of the other visits for either group.

No subject in the Nepafenac group had a shift in aqueous flare scores from normal at baseline to abnormal at any postoperative study visit.

A shift in corneal oedema scores from normal at baseline to abnormal at Day 1 was noted for 3 subjects in the Nepafenac group and 4 subjects in the Vehicle group. No subject in either treatment group had a shift in corneal oedema scores from normal at baseline to abnormal at any post-Day 1 study visit.

Corneal staining

No more than 9 subjects in any treatment group at any post-baseline study visit had a shift from normal to abnormal in corneal staining within any region and there were no trends associated with the shifts (ie., the shifts represented minor fluctuations with no obvious pattern). The mean change from baseline in corneal staining at Day 90 was approximately 0 within each region for each treatment group. There were no meaningful differences in corneal staining scores when evaluated by age category or for the overall population.

Dilated Fundus Parameters

A shift in peripheral retina scores from normal at baseline to abnormal at Day 90 was noted for 6 subjects in the Nepafenac 0.3% group and 5 subjects in the Vehicle group. A shift in macula scores from normal at baseline to abnormal at Day 90 was noted for 10 subjects in the Nepafenac 0.3% group and 21 subjects in the Vehicle group. A shift in choroid scores from normal at baseline to abnormal at Day 90 was noted for 3 subjects in the Nepafenac 0.3% group and 1 subject in the Vehicle group. Finally, 1 subject in the Nepafenac 0.3% group and 2 subjects in the Vehicle group had a shift from normal at baseline to abnormal at Day 90 in optic nerve scores. There were no meaningful differences in dilated fundus assessments when evaluated by age category or in the overall safety population.

Safety in special populations

A review of adverse events by age, gender, race and iris colour revealed no clinically relevant differences in the types and incidences of adverse events between groups for either Nepafenac 3 mg/mL or Nepafenac 1 mg/ml. The conclusions based upon a review of adverse events in these subgroups are consistent with those drawn from the review of the overall population. Similarly, no relevant differences were observed

when concomitant diseases and concomitant medication were taken into account.

A review of AEs by onset day revealed that most ocular AEs associated with the use of Nepafenac 3 mg/mL eye drops, suspension occurred within 14 days following the first dose of study medication (ie, during the immediate postoperative period).

TEAEs were not evaluated based upon extrinsic factors.

Safety related to drug-drug interactions and other interactions

No drug interactions were reported in any clinical study involving Nepafenac 3 mg/ml. Nepafenac 3 mg/ml has been safely administered in conjunction with other ophthalmic medications such as antibiotics, anesthetics, beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. Further, no drug interactions have been reported in association with several concomitant systemic medications.

Discontinuation due to adverse events

Study protocols for both C-12-067 and C12-071 encouraged subjects who discontinued treatment early to stay in the studies for follow-up. Those subjects who continued to the study end were not included in the population of study discontinuation, even though they had discontinued study medication prematurely. Previously conducted studies (C-07-43 and C-09-003) did not have the same follow-up. Therefore, an additional analysis was performed to identify subjects who discontinued study medication due to AEs regardless whether they stayed to study completion or exited from the study early.

In Nepafenac 3 mg/ml group, 6 (1.0%) subjects discontinued study medication due to AEs (4 due to eye disorders: eye irritation, macular edema, vitreous haemorrhage, vitreous loss and 2 due to injury, poisoning and procedural complications: eye injury and eye operation complication), which was lower than in the Vehicle group (20 subjects, 3.4%) and in Nepafenac 1 mg/ml group (7 subjects, 3.3%).

Post marketing experience

Nepafenac-containing products for ocular use (at concentrations of 1 mg/mL and 3 mg/mL) are authorised in 105 countries world-wide. From the first marketing authorization (August 2005) up to August 31, 2015, 41,627,878 units of Nepafenac 1 mg/ml, eye drops, suspension and 1,846,196 units of Nepafenac 3 mg/mL, eye drops, suspension have been distributed worldwide.

The cumulative postmarketing experience is in line with the reference safety information. AEs possibly associated with the ocular use of nepafenac are generally non-serious and mostly related to local ocular disorders.

2.5.1. Discussion on clinical safety

The safety assessment was mainly based on an analysis of the pooled safety data from studies C-12-067 and C-12-071. Additionally, a historical comparison between Nepafenac 3 mg/ml QD and Nepafenac 1 mg/ml TID post-cataract ME clinical trials results was provided. Given that the study population, the study design,

the treatment duration and the total daily dose (3 mg/ml) were comparable between the two strengths, this indirect comparison was found to be acceptable.

The safety population in the 4 post-cataract ME studies included 1610 patients. Among them, a total of 594 patients (301 in C-12-067 study and 293 in C-12-071 study) were exposed to nepafenac 3mg/ml and 209 patients were previously exposed in studies C-07-43 and C-09-003 to nepafenac 1 mg/ml TID.

The total treatment duration was 92 days, starting the day before the cataract surgery, 1 additional drop 30 to 120 minutes prior to the surgery on day of surgery, and during 90 days post-surgery. Around 50% of patients in studies 067 and 071 were exposed to Nepafenac 3 mg/ml for 61-90 days and the other 50% were exposed for more than 90 days. Based on the data described above, the size of the safety database as well as the extent of exposure was considered to be adequate. Even though long-term safety profile is at present unknown, this is not a concern given the intended indication.

Although similar safety results could be expected with both Nepafenac 3 mg/ml QD and Nepafenac 1 mg/ml TID administered during 92 days, the differences in the concentration of excipients (especially benzalkonium chloride) when the product is administered once daily or three times daily could have an impact on the safety profile. The intended posology for Nepafenac 3 mg/ml QD may expose patients to a less daily concentration of benzalkonium chloride (BAK) in comparison to the posology established for Nepafenac 3 mg/ml TID, which may be an advantage for Nepafenac 3 mg/ml from a safety point of view.

Indeed, based on the available clinical data, the safety profile established for nepafenac 1 mg/ml TID seems to be slightly worse than the one observed for Nepafenac 3 mg/ml. Ocular hypertension was surprisingly only reported in the current studies with Nepafenac 3 mg/ml (1% in Nepafenac 3 mg/ml vs. 0.5% in Vehicle and 0.0% in Nepafenac 1 mg/ml groups). The MAH has conducted an additional analysis in order to explore the risk of ocular hypertension associated to Nepafenac 3 mg/ml treatment. In this analysis, the related term intraocular pressure increased was also included. No meaningful differences were observed with respect to vehicle. The difference observed with respect to Nepafenac 1 mg/ml (4.9% vs 2.4% respectively) appears to be due to inter-study variation as similar differences in the reporting rates were also observed in the Vehicle arms (Nepafenac Vehicle 3 mg/ml 4.5% vs Nepafenac Vehicle 1 mg/ml 1.9%). In any event, intraocular pressure increased is mainly associated with the cataract surgery and therefore it was considered unrelated to the study drug.

Punctate keratitis, corneal oedema and intraocular pressure increased were the commonest AEs reported in patients using nepafenac 3mg/ml. All of them were associated with the surgical procedure itself. Punctate keratitis can be also associated with the ocular administration of NSAIDs and/or BAK use and was already listed as an uncommon ADR in the PI of Nevanac. Punctate keratitis and intraocular pressure incidence were similar between vehicle and active groups but corneal oedema incidence was higher in the vehicle groups compared to the active groups. It was noted that corneal oedema is not unexpected after cataract surgery and variables impacting the degree of oedema include grade of nuclear sclerosis, surgical technique, surgeon skill, pre-existing condition of the corneal endothelium, and degree of elevated IOP postoperatively.

The amount of patients reporting ADRs was considered low. Most of these AEs were local ocular AEs. The most commonly reported treatment-emergent ADRs in the nepafenac 3 mg/ml group were punctate keratitis (0.7% in Nepafenac 3 mg/ml, 1% in vehicle, 2.9% in Nepafenac 1 mg/ml), keratitis (0.3%, 0.3%, 0.0%) and foreign body sensation in eyes (0.3%, 0.5%, 0.0%). The incidences were comparable to those observed in the vehicle group. In the Nepafenac 1 mg/ml group, the incidence of punctate keratitis was slightly higher than the one reported for Nepafenac 3 mg/ml, which is likely to be associated with the BAK daily concentration.

The safety profile established for nepafenac 1 mg/ml TID seemed to be slightly worse than the one observed for nepafenac 3 mg/ml. However, ocular hypertension was only reported in the new studies with Nepafenac 3 mg/ml (1% in Nepafenac 3 mg/ml vs. 0.5% in Vehicle and 0.0% in nepafenac 1 mg/ml groups).

Given that Nepafenac 3 mg/ml is applied locally, systemic exposure to nepafenac is expected to be low. The most common non-ocular TEAEs were nasopharyngitis (1.2% in nepafenac 3 mg/ml vs. 1.8% in vehicle), intraocular pressure increased (3.9% vs. 4.0%) and headache (1.2% vs. 2.3%). Non-ocular ADRs were very few (1 patient had headache and 1 patient had vital dye staining cornea present).

No relevant safety concerns were observed during slit-lamp examinations (aqueous cells, aqueous flare, corneal oedema, bulbar redness and corneal epithelium integrity) and dilated fundus exams (peripheral, retina/macula/choroid, optic nerve).

Information related to safety in special population did not highlight any specific concern.

Data from cumulative post-marketing experience was found to be reassuring. The majority of AEs were non-serious and related to eye disorders. Dry eye was identified as a new ADR of rare frequency and added to the SmPC section 4.8. No new AE was identified from post-marketing reports.

2.5.2. Conclusions on clinical safety

The size of the safety database as well as the extent of exposure were considered sufficient to characterise the safety profile of Nepafenac 3 mg/ml in line with the proposed use in diabetic patients.

No relevant differences between the safety profile established for Nepafenac 1 mg/ml group TID and the one observed for Nepafenac 3 mg/ml were reported, which is not unexpected as the total daily dose will be the same in both cases (i.e. 3 mg/ml per day).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 8 with the following content:

Safety concerns

Important identified risks	• Hypersensitivity • Corneal disorders • Off-label use

Important potential risks	• Increased ocular bleeding
	• Potential of medication errors
	• Potential interactions:
	  ○ Interaction with topical anti-inflammatory steroids
	  ○ Additive effect with BAK
	  ○ Interaction with medicinal products which may prolong bleeding time

Missing information	• Long-term use of Nepafenac • Use in patients with concurrent ocular diseases • Use in patients using topical ocular medications • Use in paediatric patients • Use during pregnancy and lactation

Pharmacovigilance plan

Not applicable. There are no on-going or planned additional PhV studies/activities in the Pharmacovigilance Plan

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risk: Hypersensitivity	Identification in the product labelling. Contraindication in the CCDS, section 4.3, Warning in the CCDS, section 4.4 and listed event in section 4.8.	No additional risk minimization activities are needed.
Important identified risk: Corneal disorders	Identification in the product labelling. Warning in the CCDS, section 4.4, Interaction in the CCDS, section 4.5 and listed events in section 4.8.	No additional risk minimization activities are needed.
Important identified risk: Off-label use	Identification in the product labeling. The product labelling indicates the population for which the product is authorized and the method of administration, as well as the appropriate treatment duration.	No additional risk minimization activities are needed.
Important potential risk: Increased ocular bleeding	Identification in the product labelling. Warning in the CCDS, section 4.4 and Interaction in the CCDS, section 4.5.	No additional risk minimization activities are needed.
Important potential risk: Potential of medication errors	Identification in the product labeling. The product labelling indicates the population for which the product is authorized and the method of administration, as well as the appropriate treatment duration.	No additional risk minimization activities are needed.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	In order to help to differentiate the 2 strengths of NEVANAC (1 mg/ml and 3 mg/ml), 'once daily' is added on the carton for NEVANAC 3 mg/ml.	
Important potential risk: Potential interaction with anti-inflammatory steroids	Identification in the product labeling. Warning in the CCDS, section 4.4 and Interaction in the CCDS, section 4.5.	No additional risk minimization activities are needed.
Important potential risk: Additive effect with BAK	Identification in the product labeling. Warning in the CCDS, section 4.4.	No additional risk minimization activities are needed.
Important potential risk: Potential interaction with medicinal products which may prolong bleeding time	Identification in the product labeling. Warning in the CCDS, section 4.4 and Interaction in the CCDS, section 4.5.	No additional risk minimization activities are needed.
Missing information: Long-term use of Nepafenac	Identification in the product labeling. Warning in the CCDS, section 4.4 and Interaction in the CCDS, section 4.5.	No additional risk minimization activities are needed.
Missing information: Use in patients with concurrent ocular diseases	Identification in the product labeling. Warning in the CCDS, section 4.4.	No additional risk minimization activities are needed.
Missing information: Use in patients using topical ocular medications	Identification in the product labeling. Warning in the CCDS, section 4.4 and Interaction in the CCDS, section 4.5.	No additional risk minimization activities are needed.
Missing information: Use in paediatric patients	Identification in the product labeling. Warning in the CCDS, section 4.2.	No additional risk minimization activities are needed.
Missing information: Use during pregnancy and lactation	Identification in the product labeling. Warning in the CCDS, section 4.6.	No additional risk minimization activities are needed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been

updated. The Package Leaflet has been updated accordingly.

The main changes to SmPC sections 4.1, 4.2 and 4.4 are shown below (additions are shown in **bold**, deletions as ~~strike-through~~):

SmPC section 4.1

NEVANAC 3 mg/ml is indicated in adults for:

- Prevention and treatment of postoperative pain and inflammation associated with cataract surgery

- Reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients (see section 5.1)

SmPC section 4.1

For the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients, the dose is 1 drop of NEVANAC in the conjunctival sac of the affected eye(s) once daily beginning 1 day prior to cataract surgery, continued on the day of surgery and up to 60 days of the postoperative period as directed by the clinician. An additional drop should be administered 30 to 120 minutes prior to surgery.

SmPC section 4.4

~~NEVANAC 3 mg/ml eye drops, suspension should not be used for the reduction in the risk of postoperative macular edema associated with cataract surgery as efficacy and safety of this strength for this indication has not been studied.~~

In addition, the MAH took the opportunity to implement editorial changes in SmPC and to update the annexes in line with the latest QRD template.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

As the application pertains to the addition of a new indication only, the changes to the PIL were limited to some new phrases with additional information in sections 1, 3 and 4. As the format of the PIL has not changed, the readability is not expected to be affected.

3. Benefit-Risk Balance

Beneficial effects

Following administration to diabetic patients with non-proliferative retinopathy after cataract surgery, significantly fewer patients receiving Nepafenac 3 mg/ml (2.3% in Study 067 and 5.9% in Study 071) developed macular oedema compared to patients receiving Vehicle (17.3% and 14.3%, respectively). The macular thickness was substantially less in patients treated with Nepafenac than in patients treated with Vehicle (254.1 microns vs 268.2 microns [$p < 0.001$], in Study 067; 259.7 microns vs 270.0 microns [$p = 0.003$], in Study 071) at the end of treatment period. This effect was also shown in the PP analyses.

The observed effect of Nepafenac 3 mg/ml translates to 60% and 80% reduction in the odds of developing ME relative to vehicle based on C-12-071 analysis and C-12-067 + C-12-071 ad hoc pooled analysis, respectively, which was considered to be of clinical relevance.

A significant difference in the percentage of patients with an increase in BCVA of more than 15 letters was observed between groups in study 067 (18.7%; p<0.001). Moreover, a higher percentage of patients treated with Nepafenac 3 mg/ml (55.7% in Study 067 and 40.8% in Study 071) than those treated with Vehicle (44.3% and 32.4%, respectively) attained a 20/20 or better vision at the end of the study.

Uncertainty in the knowledge about the beneficial effects

Whereas the effect in terms of reduction of the incidence of macular oedema and improvement of visual acuity has been clearly established in study 067, only numerical differences have been observed in study 071.

The differences between studies have been attributed to the better than expected behaviour of the Vehicle arm (reporting an incidence of 14.3% of macular oedema, inferior to those reported in the other Nepafenac studies in this indication). This was acknowledged by the CHMP. Demographical or disease related characteristics between studies did not provide additional reasons to explain the observed differences.

All patients in the studies were treated with prednisolone eye drops for 4 weeks post-surgery. Although a synergistic effect of NSAIDs and corticosteroid has been suggested in literature (Kim, 2015), doubts regarding the benefit of additional use have also been raised (Kim. 2016). Without a control group not receiving corticosteroids a definitive conclusion regarding the role of each component of the association cannot be undoubtedly reached.

Two different SD-OCT equipments were used to measure the macular thickness and volume. In principle it should not impact on parameters expressed as relative changes (e.g the primary efficacy variable) but it might impact on those variables defined as absolute changes (e.g mean thickness of retina). The MAH has justified the lack of impact of using two different SD-OCT equipments in the main clinical trials on the final outcome by the selection of a single brand of SD-OCT by each investigational centre, the harmonization of the grading and procedures carried out by the central reading centre and the fact that the anatomic variables (those expressed as percentage of change and the measurements based upon macular volume) were relative to baseline. Although the frequency of use of the OCT equipments was different between the two studies, the distribution of equipments between treatment groups was balanced.

Risks

Unfavourable effects

The incidence of AEs reported in the clinical studies was low. The majority of TEAEs reported in all the post-cataract ME studies (C12-067, C-12-071, C-07-43, C-09-003) were local and related to eye disorders. Corneal oedema, dry eye, eye pain, foreign body sensation in eyes, ocular hypertension, punctate keratitis, intraocular pressure increased and visual acuity reduced were the most commonly TEAEs observed in the Nepafenac 3 mg/ml group with an incidence ≥ 1%.

Most of the adverse drug reactions (ADRs) were local ocular AEs. The most commonly reported treatment-emergent ADRs in the nepafenac 3 mg/ml group were punctate keratitis (0.7%), keratitis (0.3%) and foreign body sensation in eyes (0.3%). All the ADRs were already reflected in the PI of Nevanac.

Uncertainty in the knowledge about the unfavourable effects

The overall incidences of AEs were comparable to those observed in the Vehicle group and in Nepafenac 1 mg/ml TID. Some of them, such as corneal oedema and intraocular pressure increased were associated with the surgical procedure itself and were not attributed to the treatment with Nevanac. Punctate keratitis is a manifestation of mild epithelial damage and may also occur postoperatively due to the surgical procedure.

Although similar safety results are expected with both Nepafenac 3 mg/ml QD and Nepafenac 1 mg/ml TID, the differences in the concentration of excipients (especially benzalkonium chloride) when the product is administered once daily or three times daily could theoretically have an impact on the safety profile. The intended posology for Nepafenac 3 mg/ml QD may expose patients to a less daily concentration of benzalkonium chloride (BAK) in comparison to the posology established for Nepafenac 3 mg/ml TID, which may be an advantage for Nepafenac 3 mg/ml from a safety point of view. However, overall, no significant differences in the safety profiles of the two strengths have been observed.

Effects Table

Table 29 Effects Table for Nepafenac 3 mg/ml eye drops suspension administered once daily (QD) for the reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

Effect	Short Description	Unit	Nepafenac 3 mg/ml OD	Vehicle OD	Uncertainties/ Strength of evidence	References
Favourable Effects						
Prevention of Macular Oedema	Proportion of subjects who developed ME defined as an increase in CSMT of ≥ 30% relative to baseline	%	2.3 5.9	17.3 14.3	p<0.001 Difference between arms (15%) was greater than the predefined 13% difference. p<0.001 Difference of doubtful clinical relevance	Study C-12-067 Study C-12-071
BCVA improvement	Proportion of subjects with improvements in BCVA of ≥15 letters	%	61.7 48.8	43.0 50.5	p<0.001 Meaningful difference between arms (18.7%) P=0.671	Study C-12-067 Study C-12-071
Unfavourable Effects						
Corneal disorders	- Punctate keratitis - Keratitis	% %	0.7 0.3	1 0.3	Important identified risks in the RMP. Punctate keratitis and keratitis are mainly associated with the surgical procedure, nepafenac and/or BAK use.	Table 8 (SCS)

BCVA Best Corrected Visual Acuity
CSMT Central Subfield Macular Thickness
ME Macular Oedema

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Both main studies demonstrated a reduction in the risk of ME occurrence in the Nepafenac 3 mg/ml group compared to the Vehicle group. Post hoc analyses from studies C-12-067 and C-12-071 showed that reducing the risk of ME occurrence is indeed beneficial for patients in achieving better visual outcomes. Patients developing macular oedema, regardless the treatment received achieved poorer results (lower rate of patients with ≥ 15 letters improvement [22.0% in Study 067, 33.9% in Study 071] and higher rate of patients with > 5 letters worsening [50.8% and 35.6%, respectively]) than those patients without macular edema (improvement of ≥ 15 letters 55.5% and 51.4% [in Study 067 and Study 071, respectively] and worsening of > 5 letters 18.2% and 15.7% [in Study 067 and Study 071, respectively].

Although study 071 has shown only numerical difference between treatment groups, without reaching the predefined difference of 13%, additional analyses and historical comparison with studies conducted with Nevanac 1mg/mL, provided sufficient reassurance that the benefits shown for Nevanac 3mg/mL are clinically relevant.

The majority of unfavourable effects were related to eye disorders. Punctate keratitis was the most frequent TEAE associated with nepafenac administration, which is not unexpected given that this event is a well-known class-effect related to the use of ophthalmic NSAIDs. In addition, punctate keratitis may be linked with frequent and continued use of BAK. Some other common AEs (corneal oedema, intraocular pressure) were associated with the cataract surgery itself. In general, all the AEs were manageable.

Benefit-risk balance

Based on the available data, the CHMP concluded that the benefits of Nevanac 3mg/mL QD in the prevention of macular oedema following cataract surgery in diabetic patients outweighed its risks. The benefit-risk balance was thus considered favourable.

Discussion on the Benefit-Risk Balance

The sought indication is already approved for the lower strength of the same product (Nevanac 1 mg/mL). Both strengths can be considered similar in the total daily dose of Nepafenac delivered and there is no reason to expect a different response from both formulations. Rather, Nevanac 3 mg/mL represents a reduction of the burden of the treatment to the patient as it only requires once daily instillation compared to 3 times daily administration for Nevanac 1mg/ml.

The safety profile of Nepafenac 3 mg/ml QD in the prevention of postoperative macular oedema did not seem to differ from that already known for Nepafenac 1 mg/ml TID. No new safety concerns were identified for Nepafenac 3mg/ml dosed QD for 90 days postoperatively and overall safety was comparable to its vehicle and to Nepafenac 1 mg/ml TID. The potential for harm in terms of serious adverse events was very low with Nepafenac 3 mg/ml (none of the SAEs reported in C-12-067 and C-12-071 were assessed as related to study treatment). Taking into account the benign safety profile, and the convenience of once a day dosing, the CHMP agreed that Nevanac 3mg/mL provides clinically relevant benefits that outweigh the potential risks for use in the proposed indication.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include the indication 'reduction in the risk of postoperative macular oedema associated with cataract surgery in diabetic patients' also for the 3 mg/ml strength based on data from the phase III studies C-12-067 and C-12-071. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in SmPC and to update the annexes in line with the latest QRD template. An updated RMP version 8 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, labelling and Package Leaflet and to the Risk Management Plan (RMP).