Sponsor

Alcon Research, Ltd.

Generic Drug Name

Nepafenac

Trial Indication(s)

Prevention of macular edema following cataract surgery in patients with diabetic retinopathy.

Protocol Number

C-09-003

Protocol Title

A Clinical Safety and Efficacy Comparison of NEVANAC® 0.1% to Vehicle Following Cataract Surgery in Diabetic Retinopathy Patients

Clinical Trial Phase

Phase IIIb

Study Start/End Dates

04 August 2009 / May 19, 2011 (Date of Early Termination) / 10 August 2011 (Study Completion Date)

Reason for Termination

As a result of patient recruitment difficulties, Alcon elected to terminate enrollment in the study, meaning that no new patients were to have been screened or enrolled after that point. Patients who had been randomized and were undergoing treatment were allowed, at the discretion of the Investigator, to complete the study as planned.

Study Design/Methodology

The design was prospective, multicenter, randomized, double-masked, parallel-group, vehicle-controlled.

Centers

Subjects were recruited from 32 investigational sites in the United States (4), Europe (23), Israel (3), New Zealand (1), and India (1).

Objectives

The primary objective was to demonstrate the superiority of NEVANAC (nepafenac ophthalmic suspension), 0.1% (Nepafenac) relative to nepafenac ophthalmic suspension vehicle (Vehicle) based on the percentage of diabetic retinopathy patients who developed macular edema (ME) within 90 days following cataract surgery.

Test Product, Dose, and Mode of Administration

Test Product: NEVANAC (nepafenac ophthalmic suspension), 0.1% (Nepafenac)
Dose: One drop was instilled in the study eye 3 times daily (morning, midafternoon, and bedtime)
Mode of Administration: Topical ocular

Reference Product: Nepafenac ophthalmic suspension vehicle (Vehicle)
Dose: One drop was instilled in the study eye 3 times daily (morning, midafternoon, and bedtime)
Mode of Administration: Topical ocular

Statistical Methods

The primary efficacy variable (the percentage of patients who developed ME within 90 days following cataract surgery), was summarized by treatment group. The treatment groups were compared using a chi-square test of independence. Primary study inferences were based on the test of superiority conducted with the Intent-to-Treat (ITT) analysis set. Statistical inferences were drawn at a 2-sided alpha level of 0.05.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Patients were 18 years of age and older, of any race and either sex, who had a cataract and were planning to undergo cataract extraction by phacoemulsification with the implantation of a posterior chamber IOL into the lens capsule

- History of Type 1 or Type 2 diabetes
- History of nonproliferative diabetic retinopathy (NPDR), mild, moderate, or severe, in the study eye as defined by the International Clinical Diabetic Retinopathy Disease Severity Scale
- Able to understand and sign an informed consent approved by an IRB/IEC
- Central subfield macular thickness less than or equal to 320 µm in the study eye prior to cataract surgery
- Absence of clinically significant macular edema in the study eye as detected by clinical exam

Exclusion Criteria:

- Signs of vitreomacular traction or epiretinal membrane in the study eye as detected by the reading center or Investigator
- Current or previous ocular disease other than diabetic retinopathy in the study eye that, in the opinion of the Investigator, would have confounded the assessments of the macula, the retina, or central vision
- Planned multiple procedures for the study eye during the cataract/IOL implantation surgery (e.g., trabeculoplasty, corneal transplant)
- Corneal transplant in study eye
- Baseline cumulative corneal fluorescein staining score (i.e., sum of scores for all 5 corneal regions) for the study eye greater than or equal to 5, or baseline corneal fluorescein staining score in any single region for the study eye greater than or equal to 3

Participant Flow Table

	Nepafenac	Vehicle
Started (Randomized to treatment)	87	88
Safety Analysis Set	83	83
ITT Analysis Set	80	80
Completed	59	47
Discontinued	21	33
Reason for discontinued		
Adverse event	4	7
Lost to follow-up	1	2
Patient's decision unrelated to an adverse event	1	0
Noncompliance	2	1
Treatment failure	3	14
Discontinued Prior to Surgery	0	2

	Nepafenac	Vehicle
Patient did not meet entrance criteria	1	0
Patient decision	1	1
Non compliance	0	3
Study terminated	1	1
Withdrew consent	1	1
Reason not specified	6	1

Baseline Characteristics

Gender Demographic Statistics
(Intent to Treat)

Gender	Nepafenac	Vehicle
Male	51	44
Female	29	36

Categorical Age Demographic Statistics
(Intent to Treat)

Age	Nepafenac	Vehicle
<65	28	22
≥65	52	58

Summary of Efficacy

Although the sample size was reduced because the study was terminated early for reasons unrelated to safety or data, the results demonstrate a benefit relative to vehicle.

Primary Outcome Results

Number and Percent of Patients Who Developed Macular Edema within 90 Days Following Cataract Surgery (Intent to Treat)

Nepafenac			Vehicle			p-value*
Total	N	(%)	Total	N	(%)	
80	4	(5.0)	80	14	(17.5)	0.012

Macular Edema: ≥ 30% increase from baseline in central subfield retinal thickness
*Using chi-square test

Secondary Outcome Results

Best Corrected Visual Acuity (BCVA) Change (Number of Letters Read) from Baseline to Day 90/Exit Visit (Intent to Treat)

Statistic	Nepafenac N = 79	Vehicle N = 79	p-value*
	Total	Total	
Mean	17.7	14.3	0.136
SD	14.6	13.9	
(Min, Max)	(-10, 72)	(-25, 58)	
95% CI	(14.4, 21.0)	(11.2, 17.4)	

SD = Standard Deviation; CI = Confidence Interval
Baseline = Baseline Visit
*Using analysis of variance model

Summary of Safety

Based on a review of AEs and ocular safety parameters measured over the course of this clinical study, no new or unforeseen safety issues were identified after extended use (up to 90 days) of Nepafenac or Vehicle following cataract surgery in a population of adult and elderly patients with diabetic retinopathy.

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Safety Results

Serious Adverse Events

Overall, 7 patients in the Nepafenac group and 4 patients in the Vehicle group experienced a total of 19 SAEs.

All Adverse Events by System Organ Class

Adverse Event	Nepafenac N = 215		Vehicle N = 217	
	N	%	N	%
RELATED				
Eye disorders				
Punctate keratitis	4	4.8	3	3.6
Corneal erosion conjunctival	1	1.2		
Conjunctival hyperaemia			1	1.2
Corneal disorder			1	1.2
Corneal oedema			1	1.2
Eye irritation			1	1.2
Keratitis			1	1.2
Skin and subcutaneous tissue disorders				
Dermatitis allergic	1	1.2		
NOT RELATED				
Cardiac disorders				
Coronary artery disease	2	2.4		
Myocardial infarction	1	1.2		
Atrioventricular block second degree			1	1.2
Eye disorders				
Corneal oedema	5	6.0	7	8.4
Punctate keratitis	3	3.6	5	6.0

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Adverse Event	Nepafenac N = 215		Vehicle N = 217	
	N	%	N	%
Dry eye	5	6.0	2	2.4
Anterior chamber cell	5	6.0		
Macular oedema	1	1.2	4	4.8
Anterior chamber flare	2	2.4	1	1.2
Corneal disorder	1	1.2	3	3.6
Visual acuity reduced	3	3.6	1	1.2
Anterior chamber inflammation	1	1.2	2	2.4
Blepharitis	2	2.4	1	1.2
Conjunctival haemorrhage	2	2.4	1	1.2
Corneal epithelium defect	2	2.4		
Corneal erosion	1	1.2		
Eye inflammation	1	1.2	1	1.2
Photopsia	1	1.2		
Retinal haemorrhage	1	1.2		
Conjunctival hyperaemia			3	3.6
Keratoconjunctivitis sicca			1	1.2
Conjunctivitis			2	2.4
Iridocyclitis			2	2.4
Lacrimation increased			2	2.4
Eye irritation			1	1.2
Eye pain			1	1.2
Foreign body sensation in eyes			1	1.2
Retinal exudates			1	1.2
Vitreous detachment			1	1.2
Gastrointestinal disorders				

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Adverse Event	Nepafenac N = 215		Vehicle N = 217	
	N	%	N	%
Diarrhoea	1	1.2		
Haemorrhoidal haemorrhage	1	1.2		
Vomiting	1	1.2		
Hepatobiliary disorders				
Cholecystitis acute	1	1.2		
Hepatic cirrhosis	1	1.2		
Cholelithiasis			1	1.2
Infections and infestations				
Localised infection	2	2.4		
Pneumonia	2	2.4		
Hepatitis C	1	1.2		
Upper respiratory tract infection	1	1.2		
Pyelonephritis			1	1.2
Injury, poisoning and procedural complications				
Injury	2	2.4	1	1.2
Cataract operation complication			1	1.2
Foreign body in eye			1	1.2
Investigations				
Intraocular pressure increased	3	3.6	3	3.6
Blood potassium decreased	1	1.2		
Corneal staining			1	1.2
Blood glucose increased			1	1.2
International normalised ratio increased			1	1.2
Metabolism and nutrition disorders				
Diabetic ketoacidosis			1	1.2

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Adverse Event	Nepafenac N = 215		Vehicle N = 217	
	N	%	N	%
Gout			1	1.2
Musculoskeletal and connective tissue disorders				
Osteoarthritis	1	1.2		
Polymyalgia rheumatica	1	1.2		
Arthralgia			1	1.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Lung adenocarcinoma			1	1.2
Nervous system disorders				
Headache	1	1.2	1	1.2
Cerebral haematoma	1	1.2		
Cerebrovascular accident	1	1.2		
Renal and urinary disorders				
Renal failure acute	1	1.2		
Reproductive system and breast disorders				
Benign prostatic hyperplasia	1	1.2		
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	1	1.2		
Surgical and medical procedures				
Cataract operation	1	1.2		
Corneal operation	1	1.2		
Knee operation	1	1.2		
Vascular disorders				
Aortic stenosis	1	1.2		
Diabetic vascular disorder	1	1.2		
Hypertension	1	1.2		

Other Relevant Findings

There are no other relevant findings to disclose.

Date of Clinical Trial Report

24-Apr-2012