Sponsor

Alcon Research, Ltd.

Generic Drug Name

Nepafenac 1 mg/ml Eye Drops, Suspension

Trial Indication(s)

Prevention and treatment of ocular pain and inflammation associated with cataract surgery

Protocol Number

C-04-65

Protocol Title

Nepafenac Eye Drops, Suspension Compared to Ketorolac Trometamol 0.5% Eye Drops, Solution and Placebo (Nepafenac Vehicle) for the Prevention and Treatment of Ocular Inflammation and Ocular Pain Associated with Cataract Surgery: European Study

Clinical Trial Phase

Phase 3

Study Start/End Dates

November 29, 2005 to July 25, 2006

Reason for Termination (if applicable)

Not applicable

Study Design/Methodology

This was a multi-center, randomized, observer- and patient-masked, parallel-group, placebo- and active-controlled trial.

Centers

Subjects were recruited from 15 investigational sites located in 6 countries: France (4), Italy (3), Spain (2), Hungary (2), United Kingdom (2), and Portugal (2).

Objectives

The primary objective was to evaluate the safety and efficacy of Nepafenac 1 mg/ml Eye Drops, Suspension, compared to Placebo and Ketorolac Trometamol 5 mg/ml Eye Drops, Solution for the prevention and treatment of ocular inflammation and ocular pain after cataract extraction by phacoemulsification with posterior chamber intraocular lens (IOL) implantation

Test Product (s), Dose(s), and Mode(s) of Administration

Test Product: Nepafenac 1 mg/ml Eye Drops, Suspension
Dose: 1 drop in the study eye 3 times daily
Mode of Administration: Topical ocular

Reference Product: Ketorolac Trometamol 5 mg/ml Eye Drops, Solution
Dose: 1 drop in the study eye 3 times daily
Mode of Administration: Topical ocular

Reference Product: Placebo (Nepafenac Vehicle Eye Drops)
Dose: 1 drop in the study eye 3 times daily
Mode of Administration: Topical ocular

Statistical Methods

A chi-square test of independence was conducted to assess the superiority of Nepafenac 1 mg/ml relative to Placebo at Day 14. Primary inference for superiority was based on the intent to treat (ITT) data set.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Patients (18 years or older) of any race and either sex, requiring cataract extraction with planned implantation of a posterior chamber intraocular lens.
- Other protocol-defined inclusion criteria may apply.

Exclusion criteria:

- Under 18.
- Other protocol-defined exclusion criteria may apply.

Participant Flow Table

Subject Disposition

	Nepafenac	Ketorolac	Placebo	Total
Randomised to Treatment	77	73	77	227
Intent-to-Treat Analysis Set	76	73	76	225
Completed	72	68	62	202
Discontinued	4	5	14	23
Reason for Discontinuation				
Adverse Event	1	2	4	7
Decision Unrelated to an Adverse Event	1	0	0	1
Treatment Failure	2	3	9	14
Surgical Complications Requiring Additional Anti-Inflammatory Therapy	0	0	1	1

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Baseline Characteristics

Descriptive Statistics for Age Demographics by Treatment
(Intent-to-Treat)

Treatment	Mean	Std	N	Min	Max
Nepafenac	71.7	8.3	76	42	86
Ketorolac	72.9	9.4	73	46	87
Placebo	71.6	8.4	76	50	90
Total	72.1	8.7	225	42	90

Age Categorical Demographic Statistics by Treatment
(Intent-to-Treat)

Treatment	18-64 years		65 to 74 years		75 to 84 years		85 to 94 years	
	N	%	N	%	N	%	N	%
Nepafenac	12	15.8	32	50.0	31	48.4	1	1.6
Ketorolac	10	13.7	29	46.0	30	47.6	4	6.3
Placebo	14	18.4	33	53.2	27	43.5	2	3.2
Total	36	16.0	94	49.7	88	46.6	7	3.7

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Gender Demographic Statistics by Treatment
(Intent-to-Treat)

Treatment	Male		Female	
	N	%	N	%
Nepafenac	34	44.7	42	55.3
Ketorolac	28	38.4	45	61.6
Placebo	28	36.8	48	63.2
Total	90	40.0	135	60.0

Summary of Efficacy

The prospectively planned primary efficacy evaluation for this study was a comparison of cure rates (the absence of cells and flare) between Nepafenac and placebo, with inference based upon the Day 14 visit. In this study, patients were considered a cure at Day 14 if the sum of their aqueous cells and flare ratings was 0 (i.e., absence of cells and flare) at Day 14 and all subsequent study visits. Cure rates at the Day 3 through Day 28 visits consistently favored Nepafenac over Placebo by about 8 percentage points or more with statistical significance achieved at Day 14.

Nepafenac dosed 3 times daily was non-inferior to Ketorolac 5 mg/ml dosed 3 times daily for the treatment of ocular inflammation associated with cataract extraction and IOL implantation surgery as evidenced by similar mean aqueous cells plus flare scores at Day 21.

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Primary Outcome Result(s)

Percent Cures at Day 14 for Nepafenac versus Placebo
(Intent to Treat)

Treatment	Total N	Day 14 Clinical Cures N	Day 14 Clinical Cures %	P-Value[a]
Nepafenac	76	58	76.3	0.0241
Placebo	76	45	59.2	

a Test = Chi-square (Fishers Exact test if N<5)

Secondary Outcome Result(s)

A. Percentage of patients declared to be treatment failures (shown by Percent Clinical Successes)
B. Investigator's assessment of ocular pain
C. Percentage of patients with clinically significant inflammation
D. Eye drop comfort evaluation at the Day 7 visit

A. Percent Clinical Success by Treatment and Visit
(Intent-to-Treat)

Visit	Treatment	Total N	Clinical Successes N	Clinical Successes %	P-Value[a]
Day 1	Nepafenac	76	19	25.0	
	Ketorolac	73	20	27.4	0.7393[b]
	Placebo	76	19	25.0	1.00[c]
Day 3	Nepafenac	76	36	47.4	
	Ketorolac	73	36	49.3	0.8121[b]
	Placebo	76	31	40.8	0.4140[c]

Visit	Treatment	Total N	Clinical Successes		P-Value[a]
			N	%	
Day 7	Nepafenac	76	56	73.7	
	Ketorolac 5 mg/ml	73	51	69.9	0.6043[b]
	Placebo	76	40	52.6	0.0071[c]
Day 14	Nepafenac	76	69	90.8	
	Ketorolac	73	57	78.1	0.0319[b]
	Placebo	76	48	63.2	<.0001[c]
Day 21	Nepafenac	76	71	93.4	
	Ketorolac	73	66	90.4	0.4997[b]
	Placebo	76	59	77.6	0.0057[c]
Day 28	Nepafenac	76	72	94.7	
	Ketorolac	73	69	94.5	1.00[b]
	Placebo	76	63	82.9	0.0205[c]

[a] Test = Chi-square (Fishers Exact test if N<5)

[b] Nepafenac versus Ketorolac 5 mg/ml

[c] Nepafenac versus Placebo

B. Investigator Rating of Ocular Pain by Treatment and Visit
(Intent-to-Treat)

Visit	Treatment	Mean	Std	N	Min	Max	P-Value
Day 1	Nepafenac	0.4	0.6	76	0	2	
	Ketorolac	0.6	0.8	73	0	3	0.1695[a]
	Placebo	0.5	0.6	76	0	2	0.3917[b]
Day 3	Nepafenac	0.3	0.5	76	0	2	

	Ketorolac	0.4	0.5	73	0	1	0.1126[a]
	Placebo	0.6	0.8	76	0	3	0.0002[b]
Visit	**Treatment**	**Mean**	**Std**	**N**	**Min**	**Max**	**P-Value**
Day 7	Nepafenac	0.2	0.4	76	0	1	
	Ketorolac	0.3	0.5	73	0	1	0.3322[a]
	Placebo	0.7	0.8	76	0	4	<.0001[b]
Day 14	Nepafenac	0.1	0.4	76	0	1	
	Ketorolac	0.1	0.3	73	0	1	0.9336[a]
	Placebo	0.5	0.9	76	0	4	<.0001[b]
Day 21	Nepafenac	0.0	0.2	76	0	1	
	Ketorolac	0.1	0.3	73	0	1	0.6463[a]
	Placebo	0.4	0.7	76	0	4	0.0004[b]
Day 28	Nepafenac	0.1	0.3	76	0	2	
	Ketorolac	0.1	0.3	73	0	1	0.8556[a]
	Placebo	0.3	0.7	76	0	4	0.0103[b]

Test=Anova, Main Effect of Treatment p-value=<.0001
Treatment by Visit Interaction p-value=0.0008
a Nepafenac versus Ketorolac
b Nepafenac versus Placebo

C. Percent Significant Inflammation by Treatment and Visit

(Intent-to-Treat)

Visit	Treatment	Total N	Significant Inflammation		P-Value[a]
			N	%	
Day 1	Nepafenac	76	8	10.5	
	Ketorolac	73	8	11.0	0.9321[b]
	Placebo	76	8	10.5	1.00[c]
Day 3	Nepafenac	76	0	0.0	
	Ketorolac	73	2	2.7	0.2383[b]
	Placebo	76	8	10.5	0.0064[c]

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Visit	Treatment	Total N	Significant Inflammation		P-Value[a]
			N	%	
Day 7	Nepafenac	76	2	2.6	
	Ketorolac	73	4	5.5	0.4358[b]
	Placebo	76	9	11.8	0.0284[c]
Day 14	Nepafenac	76	3	3.9	
	Ketorolac	73	3	4.1	1.00[b]
	Placebo	76	8	10.5	0.1175[c]
Day 21	Nepafenac	76	3	3.9	
	Ketorolac	73	2	2.7	1.00[b]
	Placebo	76	8	10.5	0.1175[c]
Day 28	Nepafenac	76	3	3.9	
	Ketorolac	73	2	2.7	1.00[b]
	Placebo	76	8	10.5	0.1175[c]

a Test = Chi-square (Fishers Exact test if N<5)
b Nepafenac versus Ketorolac 5 mg/ml
c Nepafenac versus Placebo

D. Day 7 Ocular Discomfort of Drops by Treatment for Nepafenac versus Placebo
(Intent-to-Treat)

Treatment	Mean	Std	N	Min	Max	P-Value
Nepafenac	0.3	0.6	74	0	2	
Ketorolac	0.6	0.6	71	0	2	0.0158[a]
Placebo	0.4	0.6	64	0	2	0.3996[b]

Test = Two-sample t-test
16 patients had missing ocular discomfort of drops data
[a] Nepafenac versus Ketorolac 5 mg/ml
[b] Nepafenac versus Placebo

Summary of Safety

The evaluation of safety was conducted in 227 adult and elderly patients (42 to 90 years of age) who underwent cataract extraction followed by implantation of a posterior chamber intraocular lens. No deaths were reported during the study. Two serious adverse events, both assessed to be unrelated to therapy, were reported in 2 patients with exposure to Placebo (Nepafenac Vehicle) of which neither resulted in patient discontinuation. Four patients discontinued the study due to a treatment-related adverse event which included 1 patient with exposure to Nepafenac 1 mg/ml Eye Drops, Suspension (corneal precipitates coded as corneal disorder), 1 patient with exposure to Ketorolac Trometamol 5 mg/ml Eye Drops, Solution (ocular hyperemia), and 2 patients with exposure to Placebo (allergic reaction and ocular hyperemia).

Other Relevant Findings

Other Serious Adverse Events

N	Treatment	Adverse Event	Outcome	Causality Assessment	Discontinued due to the AE
1	Vehicle	Diabetes mellitus	Resolved w/Tx	Not Related	No
1	Vehicle	Retinal vein thrombosis	Continuing w/Tx	Not related	No

Other Significant Not Serious Adverse Events

N	Treatment	Adverse Event	Outcome	Causality Assessment	Discontinued due to the AE
1	Nepafenac	Corneal disorder (reported as corneal precipitates)	Resolved w/ Treatment (Tx)	Related	Yes
1	Ketorolac	Ocular hyperemia	Resolved w/Tx	Related	Yes
1	Vehicle	Allergic reaction	Resolved w/Tx	Related	Yes
1	Vehicle	Ocular hyperemia	Resolved w/Tx	Related	Yes

N	Treatment	Adverse Event	Outcome	Causality Assessment	Discontinued due to the AE
1	Ketorolac	Corneal edema	Resolved w/Tx	Not related	Yes
1	Vehicle	Conjunctival edema	Resolved w/Tx	Not related	Yes
1	Vehicle	Conjunctival edema and Ocular hyperemia	Resolved w/Tx	Not related	Yes

Date of Clinical Trial Report

01-December-2006