Sponsor

Alcon Research, Ltd.

Generic Drug Name

DuoTrav (Travoprost 40 mcg/ml + Timolol 5 mg/ml) Eye Drops, Solution

Trial Indication(s)

Decrease of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Protocol Number

C-05-25

Protocol Title

A Six-Week, Multicenter, Randomized, Double-Masked Study to Evaluate the Efficacy and Safety of Dosing Once-Daily Travoprost / Timolol in the Morning vs. Twice-Daily Dorzolamide / Timolol in Patients with Open-Angle Glaucoma or Ocular Hypertension.

Clinical Trial Phase

Phase IIIB

Study Start/End Dates

April 12, 2006 to February 6, 2007

Reason for Termination (if applicable)

Not applicable

Study Design/Methodology

This was a multicenter, randomized, double-masked, parallel group, active comparison trial in patients with open-angle glaucoma or ocular hypertension

Centers

Subjects were recruited from 37 investigational sites located in France (4), Germany (5), Hungary (13), Italy (4), Latvia (2), Poland (2), Spain (3), Turkey (1), and the United Kingdom (3).

Objectives

The primary objective of this study was to compare the IOP-lowering efficacy and safety of Travoprost 40 mcg/ml + Timolol 5 mg/ml Eye Drops, Solution (once-daily morning dosing) vs. Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution (dosed twice-daily) in patients with open-angle glaucoma or ocular hypertension.

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

Test Product: Travoprost 40 mcg/ml + Timolol 5 mg/ml Eye Drops, Solution
Dose: One drop in the study eye(s), once-daily at 9 AM
Mode of Administration: Topical ocular

For masking purpose: Placebo (Timolol vehicle)
Dose: One drop in the study eye(s), once-daily at 9 PM
Mode of Administration: Topical ocular

Reference Product: Cosopt (Dorzolamide 20 mg/ml + Timolol 5 mg/ml) Eye Drops, Solution
Dose: One drop in the study eye(s), twice-daily (9 AM and 9 PM)
Mode of Administration: Topical ocular

Statistical Methods

Primary inference for this study was based on the comparisons of mean IOP between the two treatment groups across the four on-therapy visits and times. Primary inference was based on the intent-to-treat analysis.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- 18 or older
- Diagnosis of glaucoma or ocular hypertension

- Other protocol-defined inclusion criteria may apply

Exclusion criteria:

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

Participant Flow Table

Patient Status
(All Patients Enrolled)

	DuoTrav	COSOPT	Total
	N	N	N
Started (Randomized to treatment)	157	162	319
Safety Population	157	162	319
Intent to Treat Population	154	162	316
Completed	153	160	313
Discontinued	4	2	6
Reasons for Discontinuation			
Adverse Event	4	1	5
Decision Unrelated to an Adverse Event	0	1	1

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Baseline Characteristics

Demographic Statistics by Treatment Group (Intent-to-Treat Population)

	Total		DuoTrav		COSOPT	
	N	%	N	%	N	%
Total	316	100.0	154	100.0	162	100.0
Age (years)						
18 to 64	187	59.2	89	57.8	98	60.5
65 to 74	89	69.0	44	67.7	45	70.3
75 to 84	40	31.0	21	32.3	19	29.7
Sex						
Male	122	38.6	58	37.7	64	39.5
Female	194	61.4	96	62.3	98	60.5

DuoTrav = Travoprost 40 mcg/ml + Timolol 5 mg/ml Eye Drops, Solution
Cosopt = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution

Summary of Efficacy

DuoTrav dosed once-daily produced IOP-lowering efficacy that is statistically superior to Cosopt at 9 AM assessment time, as evidenced by statistically significantly lower ($p<0.05$) mean IOP values at 9 AM time point.

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Primary Outcome Measure

Comparison of Mean IOP (mmHg)
(Intent-to-Treat Data)
DuoTrav versus COSOPT

	Baseline		Combined		Week 2		Week 6	
	9AM	4PM	9AM	4PM	9AM	4PM	9AM	4PM
DuoTrav								
Mean	26.9	25.1	16.8	16.2	17.0	16.2	16.6	16.2
N	154	154	154	154	154	154	154	154
Cosopt								
Mean	27.0	25.1	17.9	16.8	18.0	16.9	17.7	16.6
N	162	162	162	161	162	161	162	161
Difference	-0.1	0.0	-1.1	-0.6	-1.0	-0.7	-1.2	-0.5
P-value	0.6522	0.9867	0.0014	0.0901	0.0056	0.0660	0.0016	0.1924
Upper 95% CI	0.4	0.5	-0.4	0.1	-0.3	0.0	-0.4	0.2
Lower 95% CI	-0.7	-0.5	-1.7	-1.2	-1.7	-1.4	-1.9	-1.2

DuoTrav = Travoprost 40 mcg/ml + Timolol 5 mg/ml Eye Drops, Solution
Cosopt = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.

Secondary Outcome Measures

None reported.

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Summary of Safety

The evaluation of safety was conducted in 319 adult and elderly patients (21 to 84 years of age) who were randomized into the study and received at least 1 dose of study drug. No deaths or serious adverse drug reactions (treatment-related adverse events) were reported during this study. Two patients reported serious adverse events assessed as unrelated to the use of study drug.

All other adverse drug reactions (ocular or non-ocular) reported in patients in either treatment group occurred as single reports (0.6%). A review of the individual characteristics of these adverse drug reactions revealed no untoward safety issues.

Safety Results

Serious Adverse Events

Serious Adverse Event	**DuoTrav** Affected (2)/ At Risk (157)	**COSOPT** Affected (1)/ At Risk (162)	**Fatal?**	**Attributable to study drug?**
Alcohol Poisoning	1	0	No	No
Hallucination	0	1	No	No

Other Adverse Events by System Organ Class

Frequency and Incidence of Treatment-Related Adverse Events

Coded Adverse Event	DuoTrav (N=157)		COSOPT (N =162)	
	N	%	N	%
Immune system disorders				

Hypersensitivity	1	0.6	0	0.0
Nervous system disorders				
Headache	1	0.6	0	0.0
Dysgeusia	0	0.0	1	0.6
Eye disorders				
Eye Irritation	9	5.7	7	4.3
Conjunctival Hyperaemia	9	5.7	1	0.6
Ocular Hyperaemia	8	5.1	1	0.6
Eye Pruritus	3	1.9	6	3.7
Eye Pain	4	2.5	2	1.2
Foreign Body Sensation in Eyes	2	1.3	1	0.6
Conjunctivitis	1	0.6	0	0.0
Dry Eye	1	0.6	0	0.0
Vision Blurred	1	0.6	1	0.6

Blepharitis	1	0.6	0	0.0
Hypotony Of Eye	1	0.6	0	0.0
Lacrimation Increased	0	0.0	1	0.6
Cardiac disorders				
Arrhythmia	1	0.6	0	0.0
Musculoskeletal and connective tissue disorders				
Sensation Of Heaviness	1	0.6	0	0.0

Coded Adverse Events = MedDRA Preferred Term (version 10.0) presented by System Organ Class
Travoprost/Timolol = Travoprost 40 mcg/ml + Timolol 5 mg/ml Eye Drops, Solution (DuoTrav)
Dorzolamide/Timolol = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution (Cosopt)

Other Relevant Findings

No other relevant findings to disclose.

Date of Clinical Trial Report

20 May 2008