Sponsor

Alcon Research, Ltd.

Generic Drug Name

Travoprost/timolol maleate fixed combination

Trial Indication(s)

Ocular Hypertension and Primary Open-Angle Glaucoma

Protocol Number

EMD-06-02

Protocol Title

Phase IV Randomized Double-masked Clinical Trial: Assessing Morning versus Evening Dosing of a Fixed Dose Combination of Travoprost 0.004% / Timolol Maleate 0.5% in Patients with Primary Open-angle Glaucoma or Ocular Hypertension

Clinical Trial Phase

IV

Study Start/End Dates

30-October-2008 to 02-June-2010

Reason for Termination (if applicable)

Not applicable

Study Design/Methodology

This was a prospective, multi-center, randomized, double-masked, parallel study.

Centers

Subjects were recruited from 6 investigational sites located in the United Kingdom.

Objectives

The primary objective was to assess the Intraocular pressure (IOP)-lowering efficacy at 9 am, 11 am and 4 pm of a fixed combination of travoprost 0.004% / timolol maleate 0.5% dosed in the morning versus the same fixed combination dosed in the evening, in subjects with open-angle glaucoma or ocular hypertension, who have an IOP insufficiently controlled (IOP ≥19 to ≤28 mmHg) by prior prostaglandin analogue monotherapy.

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

Test product: Travoprost 0.004%/timolol maleate 0.5% fixed combination
Subjects self-administered the medication according to one of the following randomized schedules:
Group A:
1 drop of active medication in each eye at 9 A.M. each morning, and 1 drop of Timolol vehicle as placebo in each eye, at 9 P.M. each evening for 12 weeks
Group B: 1 drop of Timolol vehicle as placebo in each eye at 9 A.M. each morning, and 1 drop of active medication (DuoTrav) in each eye, at 9 P.M. each evening for 12 weeks

Reference product: Timolol vehicle used as placebo

Statistical Methods

All continuous variables were summarized using descriptive statistics including N, mean, SD, median, maximum, and minimum. All categorical variables were summarized using frequency counts and percentages. Efficacy analysis was performed on the Intent-to-Treat (ITT) population, with supportive analysis performed on the Per-Protocol (PP) population. Comparisons of IOP between the two groups (subjects dosed in the morning vs. subjects dosed in the evening) was performed at each of three different time points during the day: 9 A.M., 11 A.M. and 4 P.M. The null hypothesis of no difference or change from baseline for each time point was to be rejected if the resulting p-value was less than 0.05 (2-sided t-test).

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Meets protocol-specified criteria for qualification and contraception
- Voluntarily consents to participate and provides written informed consent prior to any protocol-specific procedures

Exclusion criteria:

- Use of medications outside protocol-specified parameters
- Signs, symptoms or history of any condition that, per protocol or in the opinion of the investigator, might compromise:
  1. the safety or well-being of the participant or study staff
  2. the safety or well-being of the participant's offspring (such as through or breast-feeding)
  3. the analysis of results

Participant Flow Table

Disposition of subjects
Intent to Treat (ITT) Population

	A.M. (N=17)	P.M. (N=19)	Overall (N=36)
Screened			40
Randomized	17	19	36
- Intent to Treat Population	17 (100.0%)	19 (100.0%)	36 (100.0%)
- Per Protocol Population	13 (76.5%)	15 (78.9%)	28 (77.8%)
- Safety Population	17 (100.0%)	18 (94.7%)	35 (97.2%)
- Completed Study	17 (100.0%)	17 (89.5%)	34 (94.4%)
Withdrawn Early:	0	2 (10.5%)	2 (5.6%)
- due to TEAE	0	0	0

- due to worsening eye disease	0	0	0
- due to withdrawal of consent	0	0	0
- due to lost to follow-up	0	0	0
- due to other reason	0	2 (10.5%)	2 (5.6%)

Baseline Characteristics

Continuous Age Demographic Statistics for ITT Population

	A.M. (N=17)	P.M. (N=19)	Overall (N=36)
Mean (SD)	67.5 (10.22)	67.3 (8.62)	67.4 (9.27)
Median	67.0	70.0	69.5
Min; Max	50;89	46;84	46;89

Gender Demographic Statistics for ITT Population

	A.M. (N=17)	P.M. (N=19)	Overall (N=36)
Male	8	8	16
Female	9	11	20

Summary of Efficacy

In the ITT population at week 4, 9 A.M. assessment, the mean IOP-lowering effects of DuoTrav dosed in the morning was 2.6 mmHg greater than the mean IOP-lowering effect for DuoTrav dose in the evening.

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Primary Outcome Result

Mean Change in Observed IOP in 'study eye' following DuoTrav Treatment; ITT Population
Time Frame: Baseline, Week 4, Week 12 at 9:00 A.M.

Units: mmHG

	Baseline	Week 4	Mean Change from Baseline at Week 4	Week 12	Mean Change from Baseline at Week 12
A.M. Treatment Group	27.1	16.6	-10.5	16.4	-10.7
P.M. Treatment Group	26.3	18.0	-7.9	17.4	-8.8

Mean Change in Observed IOP in 'study eye' following DuoTrav Treatment; ITT Population
Time Frame: Baseline, Week 4, Week 12 at 11 A.M.

Units: mmHG

	Baseline	Week 4	Mean Change from Baseline at Week 4	Week 12	Mean Change from Baseline at Week 12
A.M. Treatment Group	25.2	17.6	-7.5	16.6	-8.5
P.M. Treatment Group	26.1	18.2	-7.5	17.1	-9.0

Mean Change in Observed IOP in 'study eye' following DuoTrav Treatment; ITT Population
Time Frame: Baseline, Week 4, Week 12 at 4:00 P.M.

Units: mmHG

	Baseline	Week 4	Mean Change from Baseline at Week 4	Week 12	Mean Change from Baseline at Week 12
A.M. Treatment Group	25.1	17.5	-7.6	17.7	-7.4
P.M. Treatment Group	25.7	18.2	-7.1	16.2	-9.3

Secondary Outcome Result

None reported.

Summary of Safety

All subjects showed a safety profile consistent with the particular patient population and with topical treatment with DuoTrav. There were no notable differences in TEAEs presented by subjects treated with DuoTrav in the morning compared to those treated with DuoTrav in the evening.

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Safety Results

Serious Adverse Events by System Organ Class

Summary of Treatment-Emergent Serious Adverse Events Systemic Events
(Safety Population)

System Organ Class Preferred Term	A.M. (N=17)	P.M. (N=18)	Overall (N=35)
Number (%) of Subjects Reporting SAEs	1(5.9%)	0	1(2.9%)
Immune system disorders	1(5.9%)	0	1(2.9%)
Drug hypersensitivity	1(5.9%)	0	1(2.9%)
Nervous system disorders	1(5.9%)	0	1(2.9%)
Syncope	1(5.9%)	0	1(2.9%)

Other Adverse Events by System Organ Class

Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Systemic Events (Safety
Population)

System Organ Class Preferred Term	A.M. (N=17)	P.M (N=18)	Overall (N=35)
Number of AEs : Number (%) of Subjects Reporting Any AEs	7:5(29.4%)	7:3(16.7%)	14:8(22.9%)
Gastrointestinal disorders	0	4:2(11.1%)	4:2(5.7%)
Abdominal pain upper	0	1:1(5.6%)	1:1(2.9%)
Food poisoning	0	1:1(5.6%)	1:1(2.9%)
Nausea	0	1:1(5.6%)	1:1(2.9%)
Vomiting	0	1:1(5.6%)	1:1(2.9%)

Infections and infestations	1:1(5.9%)	0	1:1(2.9%)
Viral upper respiratory tract infection	1:1(5.9%)	0	1:1(2.9%)
Investigations	0	1:1(5.6%)	1:1(2.9%)
Blood pressure systolic increased	0	1:1(5.6%)	1:1(2.9%)
Metabolism and nutrition disorders	0	1:1(5.6%)	1:1(2.9%)
Decreased appetite	0	1:1(5.6%)	1:1(2.9%)
Musculoskeletal and connective tissue disorders	2:2(11.8%)	0	2:2(5.7%)
Muscular weakness	1:1(5.9%)	0	1:1(2.9%)
Osteitis	1:1(5.9%)	0	1:1(2.9%)
Nervous system disorders	3:3(17.6%)	0	3:3(8.6%)
Amnesia	1:1(5.9%)	0	1:1(2.9%)
Headache	1:1(5.9%)	0	1:1(2.9%)
Vascular disorders	0	1:1 (5.6%)	1:1 (2.9%)
Hypertension			

Other Relevant Findings

There are no other relevant findings to disclose.

Date of Clinical Trial Report

31-October-2011