Sponsor

Alcon Research, Ltd.

Generic Drug Name

Travoprost APS

Trial Indications

Open-angle glaucoma or ocular hypertension

Protocol Number

C-09-001

Protocol Title

An Evaluation of Patient Reported Outcomes and Ocular Surface Health in Patients Using Travoprost APS Eye Drops Solution Versus XALATAN® Eye Drops Solution

Clinical Trial Phase

Phase III

Study Start/End Dates

27 May 2009 / 18 February 2011 (Date of Early Termination) / 25 May 2011 (Study Completion Date)

Reason for Termination

Study Design/Methodology

The design was parallel group, multicenter, double masked, randomized, active control.

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C-09-001 was originally designed to use Ocular Surface Disease Index (OSDI) scores to evaluate Travoprost APS and XALATAN in patients with open-angle glaucoma or ocular hypertension at the end of the 3-month treatment. The protocol was amended to use the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) to assess changes in visual acuity that can occur due to the effects of preservative on the cornea.

Centers

Under the Protocol Version 1, participants were recruited from 16 investigational sites located in the United States (12), Australia (2), Singapore (1), and Italy (1).
Under Protocol Version 2, participants were recruited from 31 investigational sites located in Australia (4), Lithuania (2), Latvia (2), Singapore (3), Italy (3), Belgium (2), Brazil (6), Hungary (3), Sweden (4), and the United Kingdom (2).

Objectives

The primary objective of the amended study was to understand differences in visual function-related patient-reported outcomes between a non-benzalkonium chloride (BAK) medication (Travoprost APS) and a BAK-preserved medication (XALATAN) as measured by the 25 Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) in patients with open-angle glaucoma or ocular hypertension.

Test Product, Dose, and Mode of Administration

Test Product: Travoprost APS (alternate preservative system) 40 micrograms/ml Eye Drops, Solution (Referred to as Travoprost APS)
Dose: 1 drop in the study eye(s) once daily each evening at approximately 21:00 hours
Mode of Administration: Topical ocular

Reference Product: XALATAN (latanoprost 50 micrograms/ml) Eye Drops, Solution
Dose: 1 drop in the study eye(s) once-daily each evening at approximately 21:00 hours
Mode of Administration: topical ocular

Statistical Methods

Analysis of the primary efficacy variable, mean NEI VFQ-25 composite (Visual Function) score at the end of the treatment period (Day 90), was performed using descriptive statistics (mean, standard deviation, N, minimum, maximum) for the NEI VFQ-25 composite score by treatment and day. A two-sample t-test was used to test for differences between treatments in the mean scores.

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Must have a clinical diagnosis of open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component), or ocular hypertension in at least 1 eye
- Must be willing and able to discontinue use of any topical ocular medication other than the study medication for the duration of the study
- Must have had Intraocular Pressure (IOP) controlled with mono-therapy using XALATAN® for at least 1 continuous month prior to Visit 1
- Women of childbearing potential must meet all of the following conditions at Visit 1:
    - They are not breast-feeding
    - They have a negative urine pregnancy test at Visit 1
    - They agree to undertake a urine pregnancy test upon entering and exiting the study
    - They are not planning to become pregnant during the course of the study
    - They are currently using, and agree to use adequate birth control methods for the duration of the study
- Other protocol-specified inclusion criteria may apply

Exclusion criteria:

- Any abnormality preventing reliable applanation tonometry in the study eye(s).
- Presence of any ocular pathology in either eye seen during the slit lamp or fundus exam that in the opinion of the Investigator may preclude the safe administration of test article or safe participation in this study.
- Dry eye or keratoconjunctivitis sicca (KCS) which has been, or is currently being, treated with the use of punctal plugs, punctal cautery, Restasis®, or topical ocular corticosteroids.
- Patients who have undergone keratorefractive ocular laser procedures, corneal surgery or surgery to the corneal surface, including but not limited to LASIK and PRK, within 6 months prior to Visit 1.
- Patients who have undergone intraocular or extra-ocular surgery, in either eye, within 6 months prior to Visit 1.
- Any history of ocular infections or inflammatory ocular conditions within the past 3 months in either eye.
- Use of any systemic medications on a chronic basis that have not been on a stable dosing regimen for at least 30 days prior to Visit 1.
- Use of ocular medications other than XALATAN® within 7 days of Visit 1.
- Use of corticosteroids within 30 days of Visit 1.
- Use of contact lenses within 30 days of Visit 1. Concomitant use of contact lenses is also excluded for the duration of the

study.
- History of intolerance or hypersensitivity to any component of the test articles.
- Participation in an investigational drug or device study within 30 days of entering this study.
- History or evidence of corneal transplant or transplant variant procedures.
- Other protocol-specified exclusion criteria may apply.

Participant Flow Table

	Travoprost APS	XALATAN
Started	216	218
Safety Analysis Set	215	217
Intent-to-treat (ITT) Analysis Set	152	153
Completed	200	208
Discontinued	16	10
Reason for discontinued		
Adverse event	7	5
Patient's decision unrelated to an adverse event	2	2
Protocol violation	5	3
Reason not specified	2	0

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Baseline Characteristics

Gender Demographic Statistics for ITT Population

Gender	Travoprost APS	XALATAN
Male	45	48
Female	107	105

Categorical Age Demographic Statistics for ITT Population

Age	Travoprost APS	XALATAN
<65	69	76
≥65	83	77

Summary of Efficacy

Primary Outcome Measure

Descriptive Statistics for NEI VFQ-25 Composite Score by Treatment and Day

(ITT Data)

Day		Travoprost APS	XALATAN	p-value*
Day 0 (Baseline)	N	152	153	0.746

Day		Travoprost APS	XALATAN	p-value*
	Mean	85.8	86.2	
	SD	11.1	10.5	
	(Min, Max)	(47, 99)	(45, 100)	
	95% CI	(84.0, 87.6)	(84.5, 87.9)	
Day 90 (Exit Visit)	N	152	153	0.382
	Mean	86.1	87.2	
	SD	10.5	10.7	
	(Min, Max)	(44, 100)	(40, 100)	
	95% CI	(84.4, 87.8)	(85.5, 88.9)	

SD = Standard Deviation
CI = Confidence Interval
*Two-sample t-test
VFQ-25 had 25 items with scores that ranged from 0 (worst possible score) to 100 (best possible score).
VFQ-25 subscales were derived from the 25 items: general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. Items within each subscale were averaged together to create the 12 subscale scores.
VFQ-25 Composite Score was calculated by averaging ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision subscale scores. VFQ-25 Composite Score ranged from 0 (worst possible score) to 100 (best possible score).

Secondary Outcome Results

None reported.

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Summary of Safety

No safety issues were identified in the overall safety population that would negatively impact the favorable benefit/risk profile of Travoprost 0.004%.

Safety Results

Serious Adverse Events

Eight participants had a serious adverse event: 6 in the XALATAN group and 2 in the Travoprost APS group.

All Adverse Events by System Organ Class

	Travoprost APS N = 215		**XALATAN N = 217**	
	N	%	N	%
RELATED				
Eye disorders				
Conjunctival hyperaemia	6	2.8	3	1.4
Eye irritation	4	1.9	3	1.4
Blepharitis	3	1.4	1	0.5
Conjunctivitis	2	0.9	2	0.9
Erythema of eyelid	1	0.5	1	0.5
Eye pruritus	2	0.9	1	0.5

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	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Ocular hyperaemia	2	0.9	1	0.5
Vision blurred	1	0.5	2	0.9
Eye discharge	1	0.5	1	0.5
Growth of eyelashes	2	0.9		
Eye swelling	1	0.5		
Photophobia	1	0.5		
Visual acuity reduced	1	0.5		
Dry eye			3	1.4
Foreign body sensation in eyes			2	0.9
Immune system disorders				
Drug hypersensitivity	1	0.5		
Investigations				
Corneal staining			1	0.5

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	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Nervous system disorders				
Headache			1	0.5
Skin and subcutaneous tissue disorders				
Skin discolouration	1	0.5		
Skin hyperpigmentation	1	0.5		
NOT RELATED				
Blood and lymphatic system disorders				
Leukocytosis	1	0.5		
Cardiac disorders				
Atrial fibrillation	1	0.5	1	0.5
Angina pectoris	1	0.5		
Cardiomegaly	1	0.5		
Myocardial ischaemia			1	0.5

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	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Ventricular extrasystoles			1	0.5
Ear and labyrinth disorders				
Sudden hearing loss	1	0.5		
Eye disorders				
Visual acuity reduced	5	2.3	3	1.4
Ocular discomfort	2	0.9	1	0.5
Dry eye	2	0.9	1	0.5
Eye pain	2	0.9	1	0.5
Foreign body sensation in eyes	3	1.4		
Photophobia	1	0.5	2	0.9
Vision blurred	3	1.4		
Cataract	1	0.5	1	0.5
Conjunctival hyperaemia	1	0.5	1	0.5

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	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Eye irritation	1	0.5	1	0.5
Punctate keratitis	1	0.5	1	0.5
Blepharitis	1	0.5		
Chalazion	1	0.5		
Eye pruritus	1	0.5		
Eyelid margin crusting	1	0.5		
Retinal aneurysm	1	0.5		
Retinal vein occlusion	1	0.5		
Visual impairment	1	0.5		
Asthenopia			1	0.5
Blepharospasm			1	0.5
Conjunctival haemorrhage			1	0.5
Corneal opacity			1	0.5

	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Erythema of eyelid			1	0.5
Eyelid oedema			1	0.5
Gastrointestinal disorders				
Diarrhoea	1	0.5	1	0.5
Abdominal pain upper	1	0.5		
Dental caries	1	0.5		
Nausea	1	0.5		
Constipation			1	0.5
Peptic ulcer			1	0.5
Toothache			1	0.5
General disorders and administration site conditions				
Pyrexia	2	0.9		
Infections and infestations				

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	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Nasopharyngitis	1	0.5	3	1.4
Urinary tract infection	1	0.5	1	0.5
Bronchitis	1	0.5		
Conjunctivitis bacterial	1	0.5		
Hordeolum	1	0.5		
Influenza			1	0.5
Pneumonia			1	0.5
Investigations				
Intraocular pressure increased	3	1.4	1	0.5
Metabolism and nutrition disorders				
Dyslipidaemia	1	0.5		
Gout	1	0.5		
Hyperlipidaemia	1	0.5		

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	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Type 2 diabetes mellitus	1	0.5		
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	1	0.5	1	0.5
Arthralgia	1	0.5		
Back pain	1	0.5		
Tendonitis			2	0.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast cancer			1	0.5
Melanocytic naevus			1	0.5
Nervous system disorders				
Headache	2	0.9		
Carpal tunnel syndrome			1	0.5
Cerebral haemorrhage			1	0.5

	Travoprost APS N = 215		XALATAN N = 217	
	N	%	N	%
Dizziness			1	0.5
Renal and urinary disorders				
Renal failure acute	1	0.5		
Tubulointerstitial nephritis	1	0.5		
Respiratory, thoracic and mediastinal disorders				
Atelectasis	1	0.5		
Dyspnoea	1	0.5		
Rhinorrhoea			1	0.5
Surgical and medical procedures				
Coronary arterial stent insertion			1	0.5
Vascular disorders				
Hypertension	5	2.3	1	0.5

Other Relevant Findings

No other relevant findings to disclose.

Date of Clinical Trial Report

10-May-2012