Sponsor

Alcon Research, Ltd.

Generic Drug Name

Brinzolamide 10 mg/ml

Trial Indication(s)

Primary Open-Angle Glaucoma; Ocular Hypertension

Protocol Number

CM-05-10

Protocol Title

A double-masked, multi-dose, study of the IOP-lowering efficacy of brinzolamide 1.0% compared to placebo when added to travoprost 0.004%/timolol .05% fixed combination (TTFC) as adjunctive therapy in primary open-angle glaucoma or ocular hypertensive patients

Clinical Trial Phase

Phase 4

Study Start/End Dates

December 2007 to July 1, 2009

Reason for Termination (if applicable)

Not applicable

Study Design/Methodology

This was a prospective, double-masked, randomized, placebo-controlled, parallel group trial. Patients treated with a prostaglandin-based mono or adjunctive therapy were changed to TTFC, every day dosing, for 4 weeks. Patients with an intraocular pressure (IOP)

of 19 to 32mm Hg at 08:00 hours underwent additional measurements at 12:00 and 16:00 hours. Patients were then randomized to either placebo or brinzolamide given twice daily in addition to TTFC. At week 12, patients had their IOP measurements repeated

Centers

Subjects were recruited from 15 investigational sites located in 6 countries.

Objectives

The purpose of this study was to compare the efficacy of brinzolamide versus placebo when added to travoprost/timolol fixed combination (TTFC) in patients with uncontrolled primary open-angle glaucoma or ocular hypertension.

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

Test Product: Brinzolamide 1.0% eye drops, suspension
Dose: 1 drop in the study eye 2 times daily in addition to TTFC for 12 weeks
Mode of Administration: Topical ocular

Reference Product: Vehicle
Dose: 1 drop in the study eye 2 times daily in addition to TTFC for 12 weeks
Mode of Administration: Topical ocular

Statistical Methods

All data analyses were 2 sided and had an a-level of 0.05. The per protocol analysis was used primarily to evaluate treatment groups. The primary efficacy variable, mean diurnal IOP, was analyzed by a linear repeated measures of analysis model. Diurnal IOP was defined as the average of the 3 individual diurnal time points.

Study Population: Key Inclusion/Exclusion Criteria

Included were patients were at least 18 years of age with a clinical diagnosis of ocular hypertension, primary open-angle, exfoliation, or pigment dispersion glaucoma in at least one eye (study eye); were treated with a prostaglandin agent alone or in combination with adjunctive drugs in fixed or unfixed combinations for a minimum of 2 weeks at visit 1; demonstrated an IOP between 21 and 32mm Hg inclusive in at least one eye and ≤32mm Hg in both eyes at visit 1; had an IOP between 19 and 32mm Hg inclusive at the 08:00 hours measurement in at least one eye and ≤32mm Hg at all time points in both eyes at Visit 2; and had a best corrected visual acuity of 6/30 (20/100 Snellen, 0.7 LogMAR) or better in each eye.

Excluded were patients with presence of other primary or secondary glaucomas not listed above, any abnormality preventing reliable applanation tonometry in study eye(s), any opacity or patient uncooperativeness that restricted adequate examination of the ocular fundus or anterior chamber of the study eye(s); with concurrent conjunctivitis, keratitis, or uveitis in either eye; with intraocular conventional surgery or laser surgery in study eye(s) <3 months before visit 1; who were women of childbearing potential, who had participated in any other investigational study within 30 days before visit 1; with known medical history of allergy or sensitivity to any components of the preparations used in this trial; with a history of bronchial asthma or chronic obstructive pulmonary disease that would preclude the safe administration of a topical b-blocker; or contact lens use. Other protocol-specified exclusion criteria may have applied.

Participant Flow Table

Subject Disposition
All Enrolled

TABLE 1. Patient Disposition

	Patients (%)		
	Placebo	**Brinzolamide**	**Total**
Screened patients			203
Intent-to-treat analysis	84 (100)	79 (100)	163 (100)
Per protocol analysis	78 (93)	75 (95)	153 (94)
Patients excluded from per protocol analysis	6 (7)	4 (5)	10 (6)
Incomplete intraocular pressure data	2 (1)	0 (0)	2 (1)
Withdrawals	4 (3)	4 (4)	8 (6)
Adverse events	2 (1)	1 (1)	3 (2)
Administrative error	1 (1)	0 (0)	1 (1)
Lost to follow up	0 (0)	1 (1)	1 (1)
Ran out of study drug	0 (0)	2 (2)	2 (1)
Lack of efficacy	1 (1)	0 (0)	1 (1)

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Baseline Characteristics

Demographics by Treatment
Per Protocol

TABLE 2. Patient Characteristics – Per Protocol

Variable	Value	Patients (%)			*P*
		Placebo (N = 78)	Brinzolamide (N = 75)	Total (N = 153)	
Sex	Female	53 (68)	42 (56)	95 (62)	0.13
	Male	25 (32)	33 (44)	58 (38)	
Age (y)	< 56	14 (18)	12 (16)	26 (17)	0.08
	56-65	25 (32)	16 (22)	41 (28)	
	66-75	28 (36)	23 (31)	51 (33)	
	> 75	11 (14)	23 (31)	34 (22)	

Summary of Efficacy

Brinzolamide and placebo decreased IOP from baseline for the mean diurnal IOP and all 3 individual time points (≤0.005). In patients randomized to the brinzolamide treatment group the IOP levels for the mean diurnal IOP and at all 3 individual time points were reduced when compared with patients randomized to the placebo treatment group (≤0.017). The IOP reductions from baseline are shown in Table 4 and Figure 2. The brinzolamide treatment group had reduced IOP levels from baseline when compared with placebo for the mean diurnal IOP as well as the 08:00 and 16:00 hour time points (≤0.014). However, the 12:00 hour time point was not significant (P=0.054).

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Primary Outcome Result(s)

Mean IOP at Baseline (Week 0) and Final Visit (Week 12)
Per Protocol

TABLE 3. Mean Intraocular Pressures at Baseline (Week 0) and Final Visit (Week 12) – Per Protocol

	mm Hg ± SD						
	Placebo (N = 78)			Brinzolamide (N = 75)			
Time (h)	Baseline	Week 12	*P*	Baseline	Week 12	*P*	*P**
08:00	21.7 ± 2.4	20.0 ± 3.8	< 0.001	21.1 ± 2.1	17.9 ± 3.2	< 0.001	0.002
12:00	20.6 ± 3.4	19.4 ± 4.6	0.005	19.9 ± 2.6	17.6 ± 2.9	< 0.001	0.011
16:00	20.4 ± 3.4	19.0 ± 4.3	< 0.001	19.9 ± 2.9	17.1 ± 2.8	< 0.001	0.017
Diurnal	20.9 ± 2.7	19.4 ± 3.8	< 0.001	20.3 ± 2.0	17.5 ± 2.6	< 0.001	0.003

*Between treatments.

Summary of Safety

There were no major safety concerns in this study as both treatments were generally well tolerated. No statistically significant differences in the adverse event profile existed between treatments. Only 2 serious adverse events occurred, both in the placebo group, and were not believed to be related to the treatment. Three patients were discontinued for an adverse event, none of which was sight threatening.

This placebo-controlled study suggests that brinzolamide may be generally safely added to prior TTFC combination therapy and a further statistically significant reduction in mean diurnal IOP can be achieved in patients with ocular hypertension or primary open-angle glaucoma.

Other Relevant Findings

None reported.