A phase III, multicentre, randomized, investigator-masked, cross-over, comparative efficacy study of a generic Brinzolamide 10 mg/ml ophthalmic suspension (Azad Pharma AG) and Brinzolamide 10 mg/ml ophthalmic suspension (Azopt®, Alcon) in open-angle glaucoma and ocular hypertension patients.

Clinical Trial Identifier: 2011-003692-12

Clinical Study Sponsor: Azad Pharma AG, Bahnhofstrasse 9, CH-3125 Toffen, Switzerland
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Phase of Development:	Phase III
Study Initiation Date:	First Patient treated: 04-JUNE-2012
Study Completion:	Last Patient completed: 20-DECEMBER-2012
Date of Early Study Termination (if any):	Not applicable

OVERALL SUMMARY

SUMMARY EFFICACY RESULTS:
The mean IOP reduction of 4.6 mm Hg for Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG and 5.2 mm Hg for Azopt® (Alcon) observed in this study after 28 days of treatment is comparable to literature values for Brinzolamide in ophthalmic product (2.7 – 5 mm Hg). The difference in IOP lowering effect between the two products was not significant (p-value 0.207 > 0.05).

SUMMARY SAFETY RESULTS:
Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG and Azopt® (Alcon) were safe as shown by the low incidence of Adverse Events and the absence of Serious Adverse Events.
The ocular discomfort level after application was lower after Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG than with Azopt® (Alcon).

CONCLUSION:
The IOP reduction and the Adverse Events profile of Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG was shown to be non-inferior to Azopt® (Alcon).

STUDY DETAILS

MEDICAL CONDITION

Patients suffering from open angle glaucoma and ocular hypertension with an elevated IOP, higher than 22mmHg and lower or equal than 35 mmHg

PRIMARY OBJECTIVE

To evaluate the efficacy of Brinzolamide 10 mg/ml ophthalmic suspension (Azad Pharma AG) in lowering intraocular pressure (IOP) when compared to Azopt® ophthalmic suspension.

SECONDARY OBJECTIVES

To compare the tolerance of the test and reference products using a global comfort level score.
To compare the levels of conjunctival hyperaemia induced by test and reference product.
To evaluate the general safety of the test product compared to the reference product.

SAMPLE SIZE

Sample size was calculated to provide a 90% power that at each stage the 97.06% confidence interval of the difference in change of mean diurnal IOP from baseline to Day 29 between the two products will be within 1 mmHg, assuming a treatment effect of 4 mmHg and a standard deviation of 2.4 mmHg and no real difference between the two products.

The data of 37 patients will have to be analyzed in Stage I and up to 73 patients after Stage II. Assuming a drop-out rate of ca. 20%, 45 patients will be recruited in Stage I and another 45 patients will be recruited in Stage II, resulting in a total of up to 90 patients being recruited in this study. Assuming a drop-out rate of ca. 20% a total of up to 73 patients were intended to be recruited in this study. Since the drop-out rate was below 20%, the study was stopped prematurely after 71 patients had been screened.

STATISTICAL METHOD

The non-inferiority margin was set to 1 mm Hg for the difference in treatment effect between the test and reference product.

The statistical hypotheses for treatment comparison were:

H0: Test – Reference ≤ – 1 mm Hg (test is inferior to reference) vs.

Ha: Test – Reference > – 1 mm Hg (test is not inferior to reference)

The difference between the reference product and the test product was evaluated using mixed linear model which is appropriate for the analysis of cross-over design.

EFFICACY OBSERVATIONS

Comparing the mean diurnal IOP at day 29 to the mean diurnal IOP at Day 1 in the study eye, a reduction of 4.6 mm Hg was detected in the patient group treated with Brinzolamide 10 mg/ml ophthalmic suspension (Azad Pharma AG) (ITT, n = 61).

Patients receiving Azopt® (Alcon) showed a reduction in IOP of 5.2 mg Hg after 28 days of treatment. These values are comparable to literature values for Brinzolamide ophthalmic product (2.7 – 5 mm Hg).

		Treatment		Total
		Azad	Azopt	
Day 1: IOP mean (mmHg) - study eye	Valid N	N=61	N=61	N=122
	Mean	23.3	23.6	23.5
	Median	23.3	23.3	23.3
	Standard Error of Mean	.2	.2	.2
	Std Deviation	1.9	1.8	1.8
	Minimum	16.5	21.0	16.5
	Lower quartile	22.4	22.4	22.4
	Upper quartile	24.4	24.6	24.5
	Maximum	28.3	32.8	32.8
Day 29: IOP mean (mmHg) - study eye	Valid N	N=61	N=61	N=122
	Mean	18.7	18.4	18.6
	Median	18.5	18.3	18.3
	Standard Error of Mean	.3	.3	.2
	Std Deviation	2.7	2.7	2.7
	Minimum	14.0	12.3	12.3
	Lower quartile	17.0	16.9	16.9
	Upper quartile	19.8	19.8	19.8
	Maximum	31.3	28.8	31.3
Difference in IOP means (mmHg) Day 1 - Day 29 - study eye	Valid N	N=61	N=61	N=122
	Mean	4.6	5.2	4.9
	Median	4.5	5.0	4.8
	Standard Error of Mean	.3	.4	.2
	Std Deviation	2.6	2.9	2.7
	Minimum	-4.0	-1.8	-4.0
	Lower quartile	3.6	3.9	3.8
	Upper quartile	5.8	6.4	6.0
	Maximum	14.3	19.3	19.3

Table 1: Change in mean diurnal IOP in the study eye (ITT population, N = 64) by treatment group - Day 1 vs Day 29.

The IOP reduction of Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG was shown to be non-inferior to Azopt® (Alcon).

SAFETY OBSERVATIONS

No serious adverse events (SAE) have been reported.

Thirty seven (37) non-serious adverse events (AE) were reported during the study (Safety population SAF n = 64). 23 of these AEs were of ocular origin, whereas 14 were of systemic origin.

	Treatment				Total	
	Azad		Azopt			
	N	col%	N	col%	N	col%
Total	64	100.0%	64	100.0%	128	100.0%
no AE	56	87.5%	54	84.4%	110	85.9%
ocular AE	12	18.8%	11	17.2%	23	18.0%
systemic AE	4	6.2%	10	15.6%	14	10.9%

Table 2: Summary of adverse events: ocular/systemic (SAF, n=64).

With 11 AEs reported during Brinzolamide 10mg/ml ophthalmic suspension (Azad Pharma AG) treatment and 12 AEs reported during Azopt® (Alcon) treatment, the number of AEs were almost equally distributed among the different treatment groups.

The severity of the majority of AEs (35 out of 37) was classified as mild, only 2 were rated as moderate and none was rated as severe.

Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG and Azopt® (Alcon) were safe as shown by the low incidence of Adverse Events and the absence of Serious Adverse Events. the Adverse Events profile of Brinzolamide 10 mg/ml ophthalmic suspension Azad Pharma AG was shown to be non-inferior to Azopt® (Alcon).

OCULAR DISCOMFORT

The ocular discomfort was assessed for both eyes immediately post dose, 5, 10 and 20 minutes post dose on Day 1, Day 14 and Day 29 in both treatment periods.

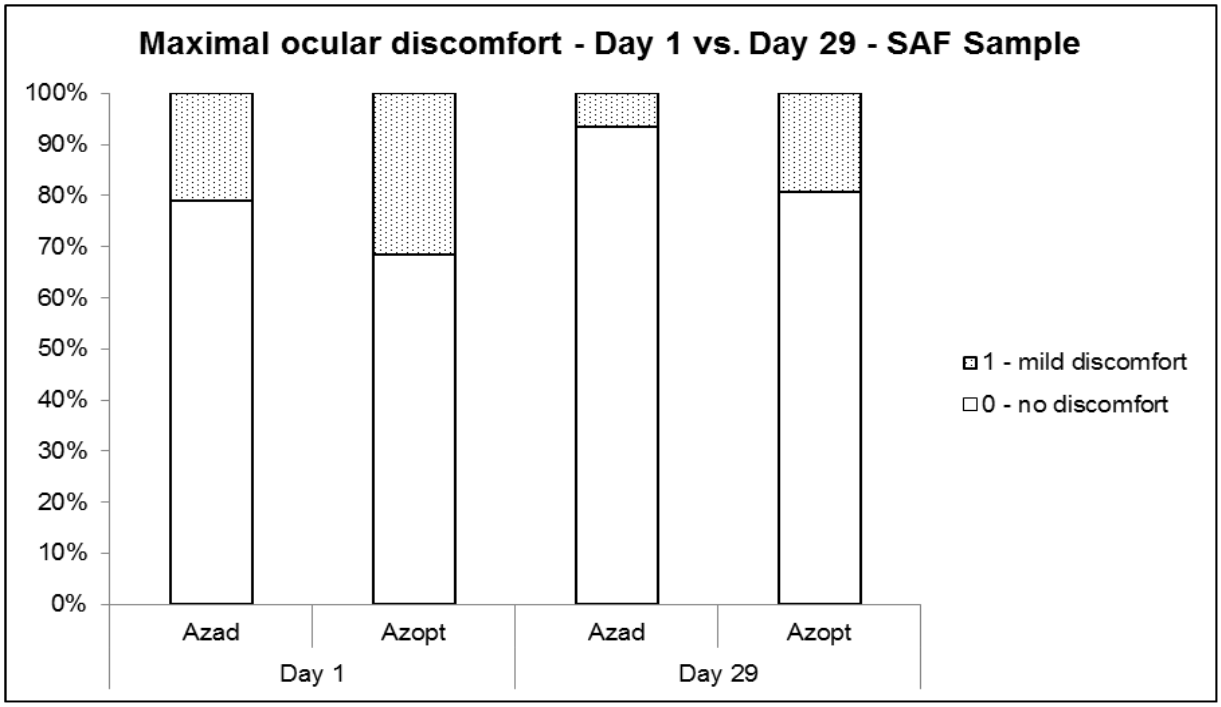

Figure 1: Maximal ocular discomfort in the study eye – Day 1 vs. Day 29 – SAF Sample

More than 76% of the patients treated with the test product Brinzolamide 10mg/ml ophthalmic suspension (Azad Pharma AG) reported no discomfort at all on Day 1. The portion of patients without discomfort increased from 76.6% to 89.1% by Day 29 while using the test product. A reduction of discomfort over time is commonly observed in ophthalmic treatments, as the procedure of application is perceived as less bothersome after repeated treatments.
Although the discomfort reported with the reference product Azopt® (Alcon) was always mild, the reference product was tolerated less as seen by the lower number of patients with no discomfort on Day 1 (67.2% versus 76.6%) and Day 29 (78.1% versus 89.1%).