European Medicines Agency

ASSESSMENT REPORT
FOR
AZOPT

International Nonproprietary Name:
BRINZOLAMIDE

Procedure No. EMEA/H/C/267/II/30

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. Introduction

Azopt (brinzolamide) 10 mg/ml Eye Drops, Suspension is a carbonic anhydrase inhibitor which reduces intraocular pressure (IOP) by inhibiting aqueous humour formation. It is intended to decrease elevated IOP in ocular hypertension and open-angle glaucoma, as monotherapy in patients unresponsive to beta-blockers or in patients in whom beta-blockers are contra-indicated, or as adjunctive therapy to beta-blockers. When used as monotherapy or adjunctive therapy, the dose is one drop of Azopt in the conjunctival sac of the affected eye(s) BID.

This variation application concerns an application for extension of the approved indication to include use of Azopt as 'adjunctive therapy' with prostaglandin analogues.

The proposed wording for the indication section is (new text highlighted **in bold**):
"*decrease elevated intraocular pressure in:*
- Ocular hypertension
- Open-angle glaucoma
as monotherapy in patients unresponsive to beta-blockers or in patients in whom beta-blockers are contra-indicated, or as adjunctive therapy to beta-blockers ***or to prostaglandin analogues.****"*

2. Clinical aspects

The basis for his variation application is the current clinical experience with patients treated with Azopt (brinzolamide) 10 mg/ml Eye Drops, Suspension as adjunctive therapy to a prostaglandin analogue, in turn based on
- three completed clinical studies of Azopt + travoprost (Travatan);
- a review of the published literature on Azopt dosed adjunctively to a prostaglandin analogue; and
- the worldwide spontaneous post-marketing reports received since the initial marketing authorisation of Azopt.

2.1 GCP

The clinical study reports (CSRs) were written in accordance with current ICH Guidelines for Structure and Content of Clinical Study Reports (E3). All clinical studies described within this submission were conducted in compliance with ICH Guidelines for Good Clinical Practice (E6) and appropriate ethical regulations. Informed consent was obtained from all the subjects participating in these clinical studies.

2.2 Clinical efficacy

The bulk of the knowledge on the efficacy of Azopt (brinzolamide) 10 mg/ml as adjunctive therapy to a prostaglandin analogue is based on three clinical studies (CM-03-06E, CM-03-06 and UK-AL0316) of Azopt + travoprost (Travatan) and a review of the published literature related to Azopt dosed adjunctively to a prostaglandin analogue. These studies are summarised in the table below, and then dealt with individually further down in this report.

One of the studies, UK-AL03016 (see below), had been assessed previously as part of a commitment relating to another eye product for which Alcon Laboratories Ltd are MAH: Travatan (travoprost) eye drops.

Table 1
Overview of Safety/Efficacy Trials with AZOPT Eye Drops, Suspension 10 mg/ml administered adjunctively to TRAVATAN

Study # (Study Type/Location)	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	# of Sites	# Patients Randomised	Status
CM-03-06 Phase IV Germany, France, Italy, Spain	Multicentre, prospective, double-masked, randomised, active-controlled, parallel group study	12 weeks	Primary open-angle glaucoma or ocular hypertension	96 – TRAVATAN and AZOPT 93 – TRAVATAN and timolol 5 mg/ml	TRAVATAN: 1 drop in the affected eye(s) at 20:00 and AZOPT: 1 drop at 8:00 and at 20:00. TRAVATAN: 1 drop in the affected eye(s) at 20:00 and timolol maleate: 1 drop at 8:00 and at 20:00.	20	253	Complete; Full/Final Report
CM-03-06E Phase IV Hungary, Romania, Slovenia, Turkey, Czech Republic, Bulgaria, Greece, Poland	Multicentre, prospective, double-masked, randomised, active-controlled, parallel group study	12 weeks	Primary open-angle glaucoma or ocular hypertension	97 – TAVATAN and AZOPT 95 – TRAVATAN and timolol 5 mg/ml	TRAVATAN: 1 drop in the affected eye(s) at 20:00 and AZOPT: 1 drop at 8:00 and at 20:00. TRAVATAN: 1 drop in the affected eye(s) at 20:00 and timolol maleate: 1 drop at 8:00 and at 20:00.	10	201	Complete; Full/Final Report
UK-AL03016 Phase IV UK	Multicentre, prospective, single arm, open label study	12 weeks	Open-angle glaucoma or ocular hypertension	82 – TRAVATAN and AZOPT	TRAVATAN: 1 drop in the affected eye(s) once daily in the evening and AZOPT: 1 drop in the affected eye(s) twice daily	7	82	Complete; Full/Final Report

Methods

Controlled studies

Two controlled clinical studies (CM-03-06E and CM-03-06) were conducted, with identical design, in which Azopt was evaluated as adjunctive therapy to Travatan for a 12-week period.

Study CM-03-06E was designed to describe the safety and efficacy of Azopt versus timolol maleate 5 mg/ml as adjunctive therapy to Travatan in patients with a clinical diagnosis of ocular hypertension or primary open-angle glaucoma (with or without pigmentary dispersion component). The study was multi-centre, randomised, double-masked, parallel group and active-controlled.

Study CM-03-06 was designed to describe the safety and efficacy of Azopt versus timolol maleate 5 mg/ml as adjunctive therapy to Travatan in patients with a clinical diagnosis of ocular hypertension or primary open-angle glaucoma. The study was multi-centre, randomised, double-masked, parallel group and active-controlled.

- Patient Population

Eligible patients were 18 years of age or older, diagnosed with ocular hypertension or primary open-angle glaucoma (with or without pigmentary dispersion component) in at least one eye. The IOP was required to be considered safe, in both eyes, to assure clinical stability of the patient's vision and optic nerve throughout the trial. Eligible patients were required to have been treated with bimatoprost, latanoprost or travoprost once daily as monotherapy for a minimum of two weeks at Visit 1 and had to have an IOP between at least 19 mmHg in at least one eye and 32 mmHg or less in both eyes. In addition, visual acuity had to be 6/60 or better in both eyes. Patients meeting inclusion criteria were substituted their current Prostaglandin analogue for Travatan monotherapy (once daily in the evening) and underwent a 4-week Travatan run-in period. Only patients whose IOP remained within the initial required range at 8 AM after the 4-week Travatan run-in were eligible to receive Azopt or timolol as adjunctive therapy.

- Key Exclusion Criteria

• Intraocular conventional surgery or laser surgery in the study eye(s) within three months prior to the screening visit.
• Progressive retinal or optic nerve disease from any cause.
• Unwillingness to accept the risk of iris colour or eyelash changes.
• A history of, or at risk for, uveitis or cystoid macular oedema (CME)

- Choice of Control Group

The studies were active-controlled with timolol maleate 5 mg/ml administered twice daily (8:00 and 20:00). The studies were double-masked inasmuch as both Azopt and timolol were supplied in identical-appearing bottles, and were dosed twice daily.

- Objective

The primary objective was to compare the efficacy and safety of timolol maleate 5 mg/ml and Azopt, each given twice daily, when added to Travatan given each evening.

- Efficacy Variables

The primary efficacy variable was the IOP measured with a Goldmann applanation tonometer for which the calibration had been verified in the previous 12 months (30 days in Study CM-03-06E).

IOP was measured at 8 AM, 12 Noon and 4 PM in studies CM-03-06 and CM-03-06E. Mean IOP, rather than change in IOP, was selected as the primary efficacy parameter in studies CM-03-06 and CM-03-06E. The primary endpoint was mean diurnal IOP, i.e., the average of the 3 IOP measurements at the Week 12 visit. Comparisons were made between the mean diurnal IOP at Week 12 for both treatment groups. Mean IOP at each time point was evaluated as secondary efficacy in both studies.

- Data Analysis

The primary efficacy variable, mean diurnal IOP, was analysed by an unpaired t-test for intra-group analysis and repeated measures of analysis. A standard deviation of 3.5 mmHg was assumed. With the planned sample size, the studies provided 80% power so that a 1.5 mmHg difference could be excluded between groups if at least 80 patients in each arm completed the study.

All patients who received study medication, had at least one on-therapy study visit and satisfied inclusion/exclusion criteria were considered evaluable for the per protocol analysis.

Uncontrolled studies

Study UK-AL0316 was designed to investigate whether there was additional IOP-lowering efficacy when Azopt is given adjunctively to Travatan for 12 weeks in patients with open-angle glaucoma or ocular hypertension, pre-treated with Travatan and requiring additional IOP-lowering therapy.

- Patient Population

Patients had to be 18 of years of age or greater, have a diagnosis of open-angle glaucoma or ocular hypertension with an IOP in one or both eyes (less than or equal to 26 mmHg). Patients had to, in the opinion of the investigator, require additional IOP-lowering following a minimum of 6 weeks monotherapy with Travatan, and would benefit from adjunctive therapy with a topical carbonic anhydrase inhibitor.

- Choice of Control Group

The patients had to have been treated with Travatan monotherapy before entry into the study and the post run-in baseline values served as the control. The study was open-label.

- Efficacy Variables

The efficacy was determined by the comparison of IOP values at baseline (Visit 1), Week 4 (Visit 2) and Week 12 (Visit 3). IOP was measured one time during each visit at not less than 2 hours or more than 4 hours after the administration of Azopt which provided an assessment of peak IOP-lowering. In

UK-AL03016, descriptive statistics were provided for the mean change in IOP from baseline. There was only one IOP measurement at each visit in this study.

- Data Analysis

The primary efficacy variable was the comparison of post-adjunctive treatment IOP values with baseline. In order to meet the objective of investigating the additive IOP-lowering effect of the combination, the efficacy endpoint was an assessment of the mean change from baseline IOP for the patient's nominated eye. Descriptive statistics were calculated for IOP at each visit, mean absolute change, mean percentage change and t-test for IOP at Week 4 and Week 12 compared with baseline.

Results

Study CM-03-06

This was a prospective, randomised, double-masked study designed to describe the safety and efficacy of AZOPT Eye Drops, Suspension versus timolol maleate when added as adjunctively to Travatan in patient with open-angle glaucoma or ocular hypertension.

- Results/Conclusions

A total of 259 subjects were included in the study and 189, randomized. Among the 64 non-randomized subjects, 55 were screening failures (*i.e.*, the IOP at eligibility visit was <19 mmHg for both eyes). The intention to treat (ITT) population included the 189 randomized subjects, 96 of which assigned to the travoprost and brinzolamide combination (brinzolamide group) and 93 to travoprost and timolol maleate (timolol group). The per-protocol (PP) population included 180 subjects; 90 assigned to travoprost and brinzolamide and 90 to travoprost and timolol maleate. The safety population included all subjects who took at least a dose of any of the study drugs, i.e. 253 subjects. Efficacy was analysed primarily in the per protocol (PP) population (180 patients (brinzolamide: N=90 and timolol: N=90).

Information regarding baseline diagnosis has not been recorded. At screening visit, most subjects were on either latanoprost (n=108) as monotherapy while fewer subjects were on travoprost (n=29) or bimatoprost (n=19). Among the non-randomised screening failures (n=55), most subjects had been on latanoprost (n=43, 78.18%), followed by bimatoprost (n=5, 9.09%) and travoprost (n=1, 1.81%) as monotherapy.

In the PP population, all individual IOPs measured at the screening and baseline visits for the worst eye were similar between both therapeutic groups. Nevertheless, at Visits 3 and 4, i.e., after 4 and 12 weeks of treatment with either study drug combinations, the 4 PM IOP reading in the timolol group was significantly lower for the worst eye (Week 4: brinzolamide: 17.87 ± 2.94 mmHg; timolol: 16.92 ± 3.01 mmHg; p=0.0325; Week 12 brinzolamide: 17.32 ± 2.79 mmHg, timolol: 16.39 ± 3.16 mmHg; p=0.0380).

Similarly to the results for the individual baseline IOPs, the baseline mean diurnal IOP was similar between both therapeutic groups (brinzolamide: 21.02 ± 2.17; timolol: 21.19 ± 2.23 mmHg). At Week 12, the mean diurnal IOP was lower in the timolol group (timolol: 17.01 ± 3.19 mmHg versus brinzolamide: 17.86 ± 2.62 mmHg) but it did not reach statistical significance (p=0.0519).

At the level of individual IOPs, the combination timolol maleate and travoprost results in significantly lower IOP at the 16:00 hour reading for the worst eye. The mean IOP in the timolol group was: 17.54 ± 3.3 mmHg at 8 AM, 17.04 ± 3.57 mmHg at 12 Noon and 16.39 ± 3.16 mmHg at 4 PM, while in the brinzolamide group, the IOP was: 18.32 ± 2.15 mmHg at 8 AM, 17.96 ± 2.72 mmHg at 12 Noon and 17.26 ± 2.81 mmHg at 4 PM.

Table 2
Mean IOP (mmHg) Comparison in Study CM-03-06
(Per Protocol)

		Brinzolamide	Timolol	*P*
08:00	N	90	90	
	Mean	18.32	17.54	0.0928
	SD	2.75	3.39	
12:00	N	90	90	
	Mean	17.96	17.09	0.0705
	SD	2.72	3.57	
16:00	N	90	90	
	Mean	17.32	16.39	0.0380
	SD	2.79	3.16	

Figure 1
Mean IOP Comparison in Study CM-03-06
(Per Protocol)

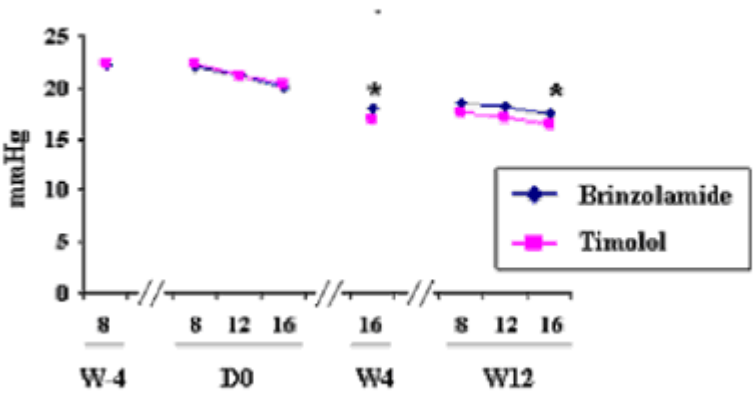


Figure 2 **Mean diurnal IOP at Baseline and Week 12 Visits**

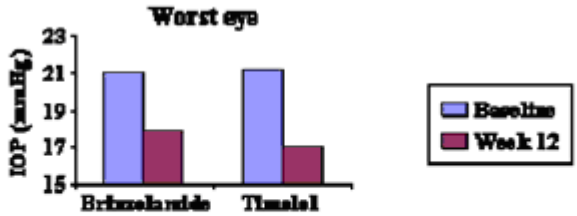
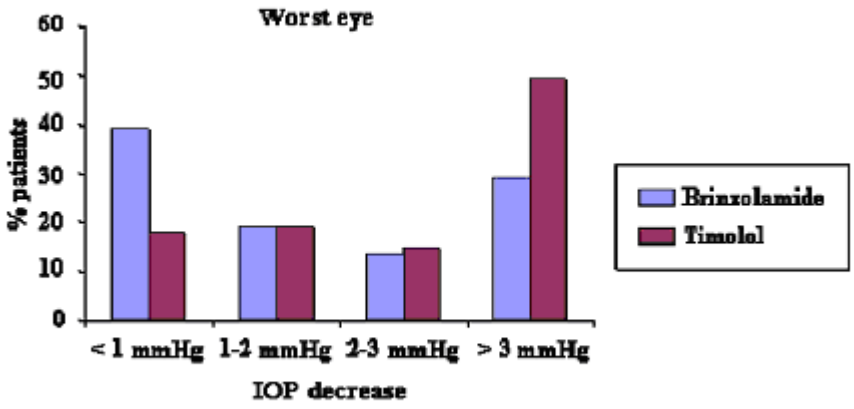


Figure 3 Subjects with IOP decrease of <1, 1-2, 2-3 and >3 mmHg between baseline and Week 4 visits



Study CM-03-06E

This was a prospective, randomised, double-masked study designed to describe the safety and efficacy of Azopt Eye Drops, Suspension versus timolol maleate when added as adjunctively to Travatan in patients with open-angle glaucoma or ocular hypertension.

- Results

A total of 215 patients were included in the study and 201 randomised. Efficacy was analysed in the per protocol (PP) population, which included 192 patients (brinzolamide: N=97 and timolol: N=95).

In terms of demographic and baseline characteristics, the subjects from both groups were similar. Most subjects were diagnosed with primary open-angle glaucoma (73.20% [n=71] in group brinzolamide and 71.58% [n=68] in group timolol maleate), while only 25.78% [n=25] in group brinzolamide and 27.39% [n=26] in group timolol maleate had ocular hypertension. At screening visit, most subjects were on either latanoprost (n=101) or travoprost (n=86) as monotherapy. Only 5 subjects had been on bimatoprost.

The baseline mean diurnal IOP was similar between treatment groups (brinzolamide: 21.5 ± 2.2 mmHg versus timolol maleate: 21.3 ± 2.5 mmHg, p=0.5).

No statistically significant difference was observed when the mean diurnal IOP at Visit 4 was compared between groups (brinzolamide: 18.1 ± 2.7 mmHg versus timolol maleate: 18.1 ± 3.0 mmHg, p=1.0). A non-inferiority test concluded that brinzolamide was non-inferior to timolol maleate. Moreover, when IOP was compared according to the corneal thickness, no differences were seen (p=0.3).

All individual IOPs measured throughout the study, including those at screening and at Visit 3, were similar between treatment groups. No statistically significant differences were seen when the IOP reduction between baseline and Visit 4 was compared between groups.

The mean diurnal IOP reduction was 3.4 ± 2.1 mmHg for the brinzolamide group and 3.2 ± 2.4 mmHg for the timolol maleate group (p=0.6). When the IOP reduction was analysed for the three different readings (8 AM, 12 Noon and 4 PM) both treatment combinations yielded similar results (Table 4).

Table 3
Mean IOP (mmHg) Comparison and Confidence Interval in Study CM-03-06E (Per Protocol)

	Brinzolamide (N=97)	Timolol maleate (N=95)	Confidence interval	Δ-value	P-value
Visit 4 08:00	19.2 ± 3.3	19.2 ± 3.6	0.0 ± 1.0	-0.5	1.0
Visit 4 12:00	17.6 ± 2.8	17.7 ± 3.3	-0.1 ± 0.9	-0.7	0.8
Visit 4 16:00	17.6 ± 3.0	17.4 ± 3.3	0.2 ± 0.9	-0.4	0.8

Figure 4
Mean IOP Comparison in Study CM-03-06E (Per Protocol)

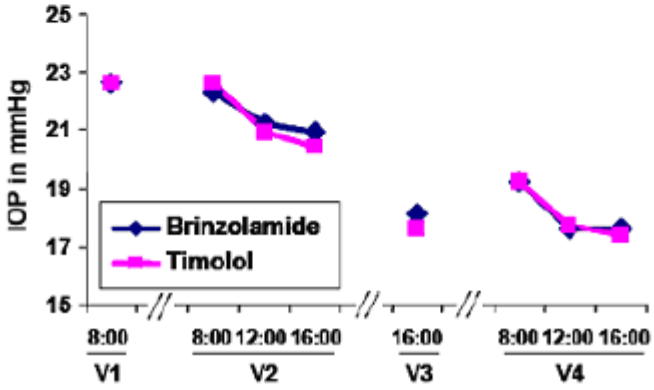


Figure 5 **Mean diurnal IOP at baseline visit and at visit 4**

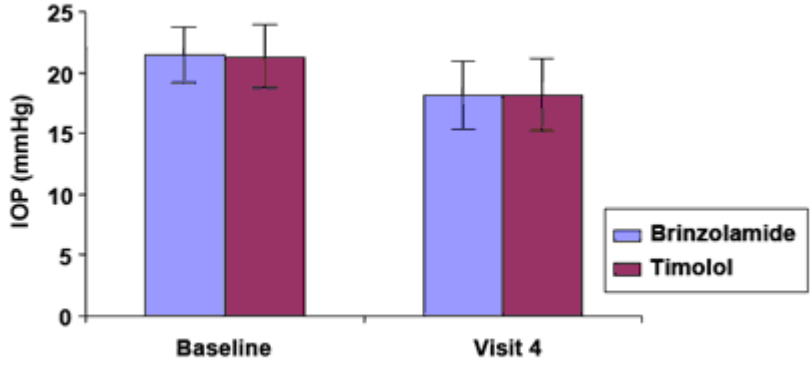


Table 4 Reduction in pressure at various time points

Time	Brinzolamide (97)	Timolol maleate (95)	P-Value
08:00	3.2 ± 2.8	3.4 ± 3.0	0.5
12:00	3.6 ± 2.7	3.1 ± 2.8	0.3
16:00	3.4 ± 2.7	3.0 ± 3.1	0.4
Diurnal	3.4 ± 2.1	3.2 ± 2.4	0.6

Open Label Study UK-AL03016

This study was a single arm, open label study. Study patients were used as their own control, with baseline data representing Travatan only treatment. Patients had a minimum of 6 weeks of Travatan monotherapy before entry into the trial. The patients' response to Travatan and Azopt combined therapy was determined by measuring the IOP at baseline (Visit 1), Week 4 (Visit 2) and Week 12 (Visit 3).

- Results/Conclusions

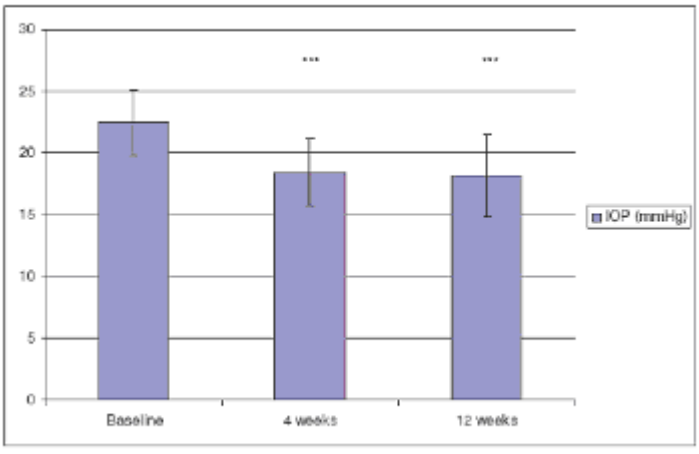
A total of 82 patients were included in the study, randomised and received at least one dose of study medication (safety population). Efficacy was analysed in the intent-to-treat (ITT) population, which included 79 patients. Compared with Travatan monotherapy, treatment with Travatan and Azopt provided a statistically significant sustained reduction in IOP, with reductions of 3.9 mmHg (17.4%, p<0.0001) after 4 weeks and 4.2 mmHg (18.4%, p<0.0001) after 12 weeks. The number of patients in whom IOP was maintained at or below 18 mmHg was increased from 5 patients (6.3%) at baseline to 43 patients (60.6%) at 12 weeks.

Table 5
Mean IOP and Change from Baseline in Study UK-AL03016 (Intent-to-Treat)

Visit	Mean IOP	N	SD
Baseline	22.5mmHg	79	2.6
Week 4	18.5mmHg	78	2.6
Week 12	18.2mmHg	71	3.3

Visit	Mean IOP Change	% Change	n
Baseline	-	-	-
Week 4	-3.9mmHg	-17.4%	78
Week 12	-4.2mmHg	-18.4%	71

Figure 6
Mean IOP (mmHg) in Study UK-AL03016 (Intent-To-Treat)



*** p<0.0001

Publications on the Use of Azopt Eye Drops, Suspension 10 mg/ml Dosed Adjunctively to a Prostaglandin Analogue

1) Martinez-de-la-Casa et al., 2004. Concomitant administration of travoprost and brinzolamide versus fixed latanoprost/timolol combined therapy: three-month comparison of efficacy and safety

Forty-four patients with primary open-angle glaucoma or ocular hypertension with elevated IOP insufficiently responsive to monotherapy were randomly assigned to one of the two treatment groups:

• concomitant administration of travoprost 40 mcg/ml once daily and brinzolamide 10 mg/ml twice daily (travoprost + brinzolamide group: 22 patients) or
• latanoprost 50 mcg/ml plus timolol 5 mg/ml once daily (latanoprost/timolol group: 22 patients).

Patients were examined at screening (current ocular hypotensive therapy was discontinued), baseline (randomisation), and after 2 weeks, 1 month, 2 months and 3 months of therapy. The objective was to compare the efficacy and safety of the concomitant administration of travoprost 40 mcg/ml once daily and brinzolamide 10 mg/ml twice daily with those of a fixed combination of latanoprost 50 mcg/ml/timolol 5 mg/ml once daily. IOP was determined at 9 AM, 12 Noon and 4 PM at each study visit, and diurnal IOP was calculated as the mean of these recordings.

Results/Conclusions
IOP at the baseline visit was similar in both groups. Overall mean IOP was significantly lower in the travoprost + brinzolamide group as compared to the latanoprost/timolol group at 1 month, 2 month and 3 months; only the 9 AM measurements were significantly different, reaching a maximum difference (16.9 ± 0.9 mmHg vs 18.4 ± 1.8 mmHg, $p<0.001$) at the month 3 visit. The percentage of responders (IOP decrease ≥30%) was higher in the travoprost + brinzolamide group.

Travoprost 40 mcg/ml and brinzolamide 10 mg/ml concomitant therapy showed a greater efficacy than the fixed latanoprost 50 mcg/ml/timolol 5 mg/ml combination in terms of absolute IOP decreases. Travoprost + brinzolamide therapy also offered the advantages of a greater percentage of responders.

2) Reis et al., 2006. A randomised, investigator-masked, 4-week study comparing timolol maleate 0.5%, brinzolamide 1%, and brimonidine tartrate 0.2% as adjunctive therapies to travoprost 0.004% in adults with primary open-angle glaucoma or ocular hypertension.

In a randomised, comparative, investigator-masked study, patients with open-angle glaucoma or ocular hypertension who were treated with travoprost 40 mcg/ml monotherapy were randomised to receive 1 of the following 3 adjunctive therapies (timolol maleate 5 mg/ml, brinzolamide 10 mg/ml, or brimonidine tartrate 2 mg/ml), 1 drop twice daily in each randomised eye, in addition to 1 drop daily of travoprost for a period of 4 weeks. IOP was measured on days 0 (travoprost 40 mcg/ml) and 28 (travoprost 40 mcg/ml and adjunctive treatment).

Results/Conclusions
In addition to continuing travoprost treatment, 20 eyes received timolol, 16 eyes received brinzolamide, and 16 eyes were treated with brimonidine. There were no significant differences among the groups in the mean IOP at baseline on day 0 (19.0 ± 4.1, 17.2 ± 3.5, and 17.0 ± 3.1 mmHg, respectively; p=NS). On day 28, the reduction in mean IOP in eyes treated with brimonidine tartrate 2 mg/ml was significantly smaller (2.3 ± 1.8 mmHg vs 3.9 ± 1.8 mmHg [p=0.01]) and the mean percentage reduction in IOP was significantly smaller (13.4% ± 9.1% vs 20.2% ± 7.5% [p=0.01]) when compared with timolol maleate 5 mg/ml, and likewise when compared with brinzolamide 10 mg/ml (4.0 ± 2.1 mmHg [p=0.02] and 22.7% ± 8.6% [p=0.006], respectively). The group treated with brinzolamide was associated with a similar reduction in IOP to timolol (p=NS for both mean IOP and percentage reduction in IOP compared with timolol monotherapy).
Brinzolamide 10 mg/ml and timolol maleate 5 mg/ml treatment were both associated with a significantly greater reduction in IOP compared with brimonidine 2 mg/ml when administered

adjunctively to travoprost 40 mcg/ml in patients with OAG and OHT whose IOP was inadequately controlled with travoprost monotherapy.

3) Shoji et al., 2005. Intraocular pressure lowering effect of brinzolamide 1.0% as adjunctive therapy to latanoprost 0.005% in patients with open angle glaucoma or ocular hypertension: an uncontrolled, open-label study

A prospective study to evaluate the intraocular pressure (IOP) lowering effect of brinzolamide 10 mg/ml ophthalmic suspension as an adjunctive therapy with latanoprost 50 mcg/ml ophthalmic solution in patients with open-angle glaucoma or ocular hypertension.

The IOP values at 1 month, 2 months, and 3 months were compared with those measured immediately before adding brinzolamide to the regimen (baseline).

Results/Conclusions
The baseline IOP was 21.1 ± 4.8 mmHg. After 1 month, 2 months, and 3 months of therapy IOP was 16.9 ± 4.5 mmHg, 16.6 ± 4.0 mmHg, and 15.9 ± 3.1 mmHg, respectively, showing significant reductions in IOP at all time-points during the study compared with the baseline value ($p<0.01$). The addition of brinzolamide to a latanoprost 50 mcg/ml regimen may further lower IOP in patients with open-angle glaucoma or ocular hypertension.

4) Tsukamoto et al., 2005a. The efficacy and ocular discomfort of substituting brinzolamide for dorzolamide in combination therapy with latanoprost, timolol, and dorzolamide.

An 8-week, prospective, randomised, open-label, comparative study of 58 patients with primary open-angle glaucoma who had been treated with latanoprost once-daily, timolol twice-daily, and dorzolamide 10 mg/ml three times daily for at least one month. These patients were randomly enrolled into one of two groups: (1) dorzolamide 10 mg/ml three times daily was substituted with brinzolamide 10 mg/ml twice-daily (substituting group); and (2) dorzolamide 10 mg/ml three times daily was continued (control group) to evaluate the efficacy and ocular discomfort of substituting brinzolamide for dorzolamide in patients with glaucoma treated by latanoprost, timolol, and dorzolamide.

Results/Conclusions
The IOPs at baseline, 4 and 8 weeks after the enrolment were 17.7 ± 2.7 mmHg, 17.5 ± 2.6 mmHg, 17.4 ± 2.9 mmHg in the substituting group, and 18.0 ± 2.5 mmHg, 17.8 ± 2.5 mmHg, and 17.9 ± 2.6 mmHg in the control group, respectively. There were no significant differences in IOP changes between the two groups ($p=0.74$). In the substituting group, ocular irritation was decreased significantly ($p=0.0014$) from 63% to 20%. The slight increase of blurred vision from 27% to 37% that occurred in the substituting group was not significant ($p=0.58$). In the control group, neither ocular irritation ($p=0.58$, from 68% to 57%) nor blurred vision ($p> 0.99$, from 25% to 21%) was changed. Substituting brinzolamide for dorzolamide maintained stable IOP with improvement in ocular comfort in patients with glaucoma.

5) Tsukamoto et al., 2005b. The efficacy and safety of topical brinzolamide and dorzolamide when added to the combination therapy of latanoprost and a beta-blocker in patients with glaucoma.

An 8-week, randomised, open-label comparative study of 52 patients with glaucoma. Brinzolamide 10 mg/ml (twice-daily) or dorzolamide 10 mg/ml (3 times daily) was randomly administered to the patients who had been treated with both latanoprost and a beta-blocker. The purpose of this study was to compare the efficacy and safety of brinzolamide 10 mg/ml versus dorzolamide 10 mg/ml when added to the combination therapy of latanoprost and a beta-blocker in patients with glaucoma.

Results/Conclusions
Intraocular pressure was decreased significantly ($p<0.0001$) from 18.6 ± 2.3 mmHg to 16.7 ± 2.3 mmHg and from 18.4 ± 2.6 mmHg to 16.6 ± 2.5 mmHg, 8 weeks after the addition of brinzolamide or dorzolamide, respectively. However, the difference between the groups was not significant ($p=0.86$).

The efficacy of brinzolamide 10 mg/ml was equivalent to dorzolamide 10 mg/ml when used as adjunctive therapy to the combination of latanoprost and a beta-blocker.

6) Feldman et al., 2007. Comparison of the ocular hypotensive efficacy of adjunctive brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%

Multicentre, parallel group, double-masked study in which patients with primary open-angle glaucoma, exfoliative glaucoma or ocular hypertension who had IOP > 18 mmHg on monotherapy with Travatan were randomised to receive adjunctive therapy with brimonidine 1.5 mg/ml dosed twice daily (N=79) or with Azopt dosed twice daily (N=84) for 3 months. IOP was measured on at 8 AM, 12 Noon and 4 PM at baseline (while patients were on monotherapy with Travatan), and Month 3. At the month 1 visit, IOP was measured at the 4PM timepoint only.

Objective

The primary efficacy variable was mean diurnal IOP at Month 3 adjusted for each patient's baseline mean diurnal IOP. All IOP measurements were performed by an examiner and a reader using a Goldmann applanation tonomer, and were performed twice per eye. If there was a difference of > 2 mmHg between the first and second measurement, a third assessment was performed and the most discrepant value was discarded. The IOP recorded was the mean of the 2 readings.

Results/Conclusions

One hundred and sixty-three patients, 69 male and 94 female, were randomised into the study, of which 84 received brinzolamide and 79 received brimonidine in addition to Travatan. There were no significant differences among the groups in the mean diurnal IOP at baseline (brinzolamide = 21.1 ± 0.29 mmHg; brimonidiine = 21.7 ± 0.33 mmHg; p=0.16). At Month 3, mean diurnal IOP was significantly lower for the brinzolamide treatment group compared to the brimonidine group (brinzolamide = 18.4 ± 0.33 mmHg; brimonidine = 19.6 ± 0.41 mmHg; p=0.019). When adjusted for baseline IOP, mean diurnal IOP was also significantly lower for the brinzolamide treatment group compared to the brimonidine group (brinzolamide = 18.6 ± 0.25 mmHg; brimonidine = 19.3 ± 0.27 mmHg; p=0.035). Significant differences were also observed for the 8 AM timepoint (brinzolamide = 19.5 ± 0.31 mmHg; brimonidine = 20.6 ± 0.33 mmHg; p=0.011) and the 4 PM timepoint (brinzolamide = 17.9 ± 0.29 mmHg; brimonidine = 18.9 ± 0.31 mmHg; p=0.012). No significant difference was observed at the 12 Noon time-point.

In summary, following 3 months of therapy, Azopt and brimonidine 1.5 mg/ml resulted in a 2.8 to 3 mmHg and a 1.7 to 2.8 mmHg, respectively, additional reduction in IOP when added to travoprost 40 mcg/ml in the patients with OAG and OHT whose IOP was inadequately controlled with travoprost monotherapy. The additional IOP lowering achieved with Azopt was significantly greater than that achieved with brimonidine.

Analysis performed across trials (pooled analyses and meta-analysis)

Study Populations

Table 6 Patient Demographics

	CM-03-06						CM-03-06E						UK-AL03016	
	AZOPT + TRAVATAN		Timolol + TRAVATAN		Total		AZOPT + TRAVATAN		Timolol + TRAVATAN		Total		AZOPT + TRAVATAN	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL Patients	**96**	-	**93**	-	**189**	-	**97**	-	**95**	-	**192**	-	**82**	-
Age mean (years)	62.7	-	65.5	-	64.1	-	63.9	-	62.2	-	63.1	-	67.0	-
Sex														
Male	35	36.5	45	48.4	80	42.3	40	41.2	35	36.8	75	39.1	42	48.8
Female	61	63.5	48	51.6	109	57.7	57	58.8	60	63.2	117	60.9	40	51.2
Race														
Caucasian	96	100	93	100	189	100	97	100	95	100	192	100	76	92.7
Black	0	0	0	0	0	0	0	0	0	0	0	0	3	3.7
Asian	0	0	0	0	0	0	0	0	0	0	0	0	2	2.4
Other	0	0	0	0	0	0	0	0	0	0	0	0	1	1.2
Iris Colour														
Blue	19	19.8	23	24.7	42	22.2	13	13.4	16	16.8	29	15.1	-	-
Brown	57	59.4	58	62.4	115	60.9	55	56.7	52	54.7	107	55.7	-	-
Green	6	6.2	6	6.5	12	6.3	3	3.1	3	3.2	6	3.1	-	-
Hazel	7	7.3	3	3.2	10	5.3	19	19.6	15	15.8	34	17.7	-	-
Other	7	7.3	3	3.2	10	5.3	7	7.2	8	8.4	15	7.8	-	-
Diagnosis														
Ocular Hypertension	-	-	-	-	-	-	25	25.8	26	27.4	51	26.6	21	25.6
Primary Open Angle Glaucoma	-	-	-	-	-	-	71	73.2	68	71.6	139	72.4	61	74.4
Pseudoexfoliation Syndrome	-	-	-	-	-	-	1	1.0	0	0	1	0.5	0	0
Pigment Dispersion Syndrome	-	-	-	-	-	-	0	0	1	1.0	1	0.5	0	0

A summary of the discontinued patients with the reasons for discontinuation is provided in Table 7. The number of discontinued patients is similar between the two treatment groups, as are the reasons for discontinuation.

Table 7
Discontinued Patients

Reason for Discontinuation	AZOPT		Timolol		Total	
	N	%	N	%	N	%
Study CM-03-06 TOTAL	**6**	**6.3**	**3**	**3.2**	**9**	**4.8**
Adverse event	2	2.1	1	1.1	3	1.6
Missed visit	1	1.0	0	0	1	0.5
Did not dose in study eye	1	1.0	0	0	1	0.5
Exclusion criteria (IOP)	1	1.0	1	1.1	2	1.1
Patient decision	1	1.0	1	1.1	2	1.1
Study CM-03-06E TOTAL	**4**	**4.0**	**5**	**5.0**	**9**	**4.5**
Non compliance	1	1.0	0	0	1	0.5
History of allergy to sulfamides	1	1.0	0	0	1	0.5
Adverse event	2	2.0	1	1.0	3	1.5
Exclusion criteria (inadequate run-in: 2, prohibited medication: 1)	0	0	3	3.0	3	1.5
Ran out of study medication	0	0	1	1.0	1	0.5
Study UK-AL03016 TOTAL	**12**	**14.6**	-	-	**12**	**14.6**
Withdrawal of consent	1	1.2	-	-	1	1.2
Screening failure	1	1.2	-	-	1	1.2
Adverse event	7	8.5	-	-	7	8.5
Other	3	3.7	-	-	3	3.7

The MAH considered that no clinically relevant differences had been observed in the IOP-lowering efficacy of Azopt based on race, age, iris colour or diagnosis.

Table 8

Mean IOP (mmHg) for TRAVATAN + AZOPT Across Studies

Study	Baseline			Week 4	Week 12		
	8 AM	12 Noon	4 PM	12 Noon	8 AM	12 Noon	4 PM
CM-03-06							
Mean IOP	21.9	21.1	20.0	17.9	18.3	18.0	17.3
Mean IOP Change	-	-	-	3.2	3.6	3.1	2.7
Mean % Change	-	-	-	15.2	16.4	14.7	13.5
N	90	90	90	90	90	90	90
CM-03-06E							
Mean IOP	22.3	21.2	20.9	17.2	19.2	17.6	17.6
Mean IOP Change	-	-	-	4.0	3.1	3.6	3.3
Mean % Change	-	-	-	18.9	13.9	17.0	15.8
N	97	97	97	97	97	97	97
UK-AL03016[a]							
Mean IOP	-	22.5	-	18.5	-	18.2	-
Mean IOP Change	-	-	-	3.9		4.2	
Mean % Change	-	-	-	17.4		18.4	
N	-	79	-	78	-	71	-

[a] IOP measured 2-4 hours after morning instillation of AZOPT, arbitrarily assigned to the 12 Noon time-point in this table

- **CHMP Assessment of Efficacy data**

The CHMP considered the appropriateness of the use of brinzolamide as an adjunctive to travoprost in those patients with insufficient IOP control while on travoprost, in the light of the above data. The sought additional indication was noted to be mainly supported by two pivotal double-blind, randomised studies (Study CM-03-06E and CM-03-06) and one supportive open label study (UK-AL0316). The additional review of the published literature related to Azopt dosed adjunctively to a prostaglandin analogue was also noted by the Committee. However, the data initially provided did not allow a conclusive assessment of the benefit/risk balance of this combination in the intended target population.

Assay sensitivity and lack of placebo arm
The CHMP pointed out that the clinical efficacy of Azopt as adjunctive therapy to Travatan had not been sufficiently proven since the clinical studies lack assay sensitivity to demonstrate differences in responses if present. Additionally, the benefit of Azopt to Travatan could not be demonstrated due to the lack of a placebo controlled trial.

In reply to the CHMP concerns, the MAH provided justifications in favour of the validity of their studies, focusing in particular on the lack of a placebo-controlled arm. However, efficacy results still showed a lower IOP reduction in the controlled arm (timolol added to travoprost) than that seen in the study supporting the use of the combination (Study C-97-73), where an additional mean IOP reduction at 8 AM of 5.7 to 7.2 was seen when travoprost was added to patients with clearly insufficient IOP control while on timolol. For a full description of Study C-97-73, please refer to the Scientific Discussion in the EPAR for Travatan, available on the EMEA website. (Further reference to this study is made in this assessment, see below).

Population not fully representative of the target population and pooling of data
Another drawback of the data provided to support the proposed additional indication related to the studied population. The population included in clinical trials did not appear fully representative of the target population for a combination IOP therapy, since the criteria to consider patients insufficiently

responsive to previous treatment was rather broad (i.e. >19mmHg at 8AM). In clinical practice, however, there might be patients for whom the addition of another IOP-lowering drug might not be indicated. As a consequence, the studied population had limited room for improvement. In the opinion of the CHMP, this was substantiated by the efficacy results, where a lower magnitude of the effect than that expected was consistently seen among studies in the comparator arm.

Even though the non-inferiority hypothesis was demonstrated for travoprost + brinzolamide, with the data provided the real magnitude of the effect in the target population could not be predicted. In order to allow comparisons with available treatment combinations and provide useful information for prescribers, the MAH was requested to analyse the proportion of patients included in the clinical trials for whom there was general agreement on the need for combined therapy (i.e. patients with baseline IOP ≥24-32mmHg at 8AM while on travoprost). Additionally, the MAH was requested to perform efficacy analyses by subgroups, according to different degrees of IOP severity at baseline (e.g. ≥19-24mmHg, ≥24-32mmHg at 8 AM). For these subgroup analyses, In order to increase the statistical power, it was suggested that the data from studies CM-03-06E and CM-03-06 would be pooled, as they have identical designs.

Additional data provided by the MAH for Study CM-03-06 (see summary tables below) showed that patients in the high IOP group would obtain maximum benefit and that the observed IOP reductions were in line with what previously seen for the combination of timolol plus travoprost.

Table 9
Subgroup Efficacy Analysis (worst eye) – Mean IOP (mmHg) ± S.D.
CM-03-06 – Per Protocol Data Set

AZOPT						
N TOTAL	90					
VISIT	Baseline		Week 12		IOP Reduction from Baseline	
Baseline IOP (mmHg) Range	Low (19-24)	High (24-36)	Low (19-24)	High (24-36)	Low (19-24)	High (24-36)
N	76	14	76	14	76	14
8 AM	21.2 ± 1.3	25.5 ± 1.7	17.9 ± 2.4	20.5 ± 3.7	3.3 ± 2.3	5.1 ± 4.5
12 Noon	20.6 ± 2.2	23.9 ± 2.8	17.6 ± 2.5	19.7 ± 3.3	3.0 ± 2.6	4.2 ± 3.6
4 PM	19.6 ± 2.5	22.5 ± 3.6	16.9 ± 2.4	19.4 ± 3.7	2.7 ± 2.4	3.1 ± 4.2
Diurnal	20.5 ± 1.7	24.0 ± 2.1	17.5 ± 2.3	19.9 ± 3.4	3.0 ± 2.1	4.1 ± 3.4
TIMOLOL						
N TOTAL	90					
VISIT	Baseline		Week 12		IOP Reduction from Baseline	
Baseline IOP (mmHg) Range	Low (19-24)	High (24-36)	Low (19-24)	High (24-36)	Low (19-24)	High (24-36)
N	69	21	69	21	69	21
8 AM	21.2 ± 1.3	25.7 ± 2.2	16.8 ± 2.8	20.0 ± 4.1	4.4 ± 2.9	5.7 ± 3.5
12 Noon	20.4 ± 2.2	23.1 ± 2.5	16.4 ± 2.9	19.2 ± 4.6	4.0 ± 2.9	3.9 ± 5.2
4 PM	19.6 ± 2.3	22.4 ± 2.6	15.8 ± 2.8	18.4 ± 3.5	3.8 ± 2.5	4.0 ± 3.0
Diurnal	20.4 ± 1.7	23.7 ± 1.9	16.3 ± 2.6	19.2 ± 3.9	4.1 ± 2.5	4.5 ± 3.5

Table 10
Subgroup Efficacy Analysis (worst eye) – P values (T-test)
CM-03-06 – Per Protocol Data Set

	P-Values					
VISIT	Baseline		Week 12		IOP Reduction from Baseline	
Baseline IOP (mmHg) Range	Low (19-24)	High (24-36)	Low (19-24)	High (24-36)	Low (19-24)	High (24-36)
8 AM	0.95	0.8	0.009	0.7	0.01	0.6
12 Noon	0.6	0.4	0.01	0.7	0.03	0.8
4 PM	0.97	0.9	0.008	0.4	0.006	0.5
Diurnal	0.8	0.7	0.005	0.6	0.006	0.7

However, the number of patients in this subgroup was too limited to enable extrapolation of these results to the target population and give a real indication on the expected benefit. Additionally, due to the limited number of patients, no conclusions on possible differences among treatment groups could be drawn.

In essence, the data provided for Study CM-03-06E still did not allow any conclusion, since there could be patients not correctly classified as "high IOP" according to the mean baseline IOP at 8AM.

The CHMP acknowledged that the need for additional IOP reduction could not only be established according to the IOP value and thus, in clinical practice, patients with IOP below 24 mmHg might be candidates to adjunctive therapy. However, this population had been consistently included in similar studies to support identical indications. Furthermore, and of great significance, the inclusion of "low IOP" patients in the pivotal studies would decrease the assay sensitivity of the study to find possible differences.

The MAH admitted that the IOP entry criteria were different in the Phase 3 study C-97-73 submitted for the registration of Travatan and the two Phase 4 studies (CM-03-06 and CM-03-06E) submitted with this variation for Azopt. However, they pointed out a fundamental difference in the treatment paradigm between the Travatan and the Azopt studies. At the time study C-97-73 was designed and conducted, beta-blocking agents (and more specifically Timolol 5 mg/ml) were the most widely prescribed class of medications approved for first-line treatment of elevated IOP. Within a few years, prostaglandin analogue such as Travatan became prescribed extensively as first-line monotherapy. This is reflected in the design of the three studies submitted in the context of this variation application: in C-97-73, Travatan was added to patients insufficiently controlled on Timolol 5 mg/ml monotherapy, whereas in CM-03-06 and CM-03-06E, Timolol 5 mg/ml was added to patients insufficiently controlled on Travatan. As a result, in as much as the IOP-lowering potential of prostaglandin analogues significantly exceeds that of beta-blocking agents, it should not, in the MAH opinion, be surprising that the adjunctive effect of Timolol 5 mg/ml in CM-03-06 and CM-03-06E is smaller than the adjunctive effect of Travatan in C-97-73, despite the unfixed combination being the same.

The MAH also pointed out that for CM-03-06E, only one IOP measurement was taken per eye and the IOP at all time points was determined as the average of the measurements from both eyes. On the other hand, for CM-03-06, a worse eye analysis was conducted wherein the worse eye was the eye with the higher IOP at the 8 AM time point at the baseline visit. If both eyes were equal, then the right eye was taken as the worse eye for the analyses. The low IOP group was defined as patients having baseline IOP of <24 mmHg at 8AM in the worse eye and the high IOP group is defined as patients having baseline IOP of ≥24 mmHg at 8AM in the worse eye.

In addition, the MAH explained that for CM-03-06E, in an analysis submitted as part of this procedure, the mean IOP of the two eyes was used for the analysis, rather than the worse eye which was the planned analysis. In comparison, for CM-03-06, the IOP used for the analysis was the mean IOP of the worse eye (as identified at baseline, at the 8AM time point). As the mean between the two eyes was selected as unit of the analyses, patients D2 and D8, who had protocol violation affecting the right eye, were excluded from a PP analysis previously submitted.

The data were therefore re-analysed to ensure uniformity of assumptions: all ITT and PP analyses have been conducted using the worse eye rather than mean of the two eyes as the unit of analysis (worse evaluable eye in the case of the PP analyses). Therefore, for CM-03-06E, patients D2 and D8 who had the left eye eligible per protocol (based on the inclusion/exclusion entry criteria) were included in the PP analyses. Furthermore, patients exited prior to the week 12 visit have not been included in the PP analyses conducted on week 12 data (presented herein), although they remain included in the analysis for the visits that they have attended. The final patient disposition for CM-03-06E is presented in the table below.

Table 11:
CM-03-06E - Disposition of Patients (worse eye)

	Randomised	PP Analyses ITT minus protocol violations or no Week 12 visit data (Patient Number))
TRAVATAN + AZOPT		
Low IOP	70	69 (H14)
High IOP	31	28 (D14, H26, B20)
Total	101	97
TRAVATAN + Timolol		
Low IOP	64	60 (D4, F2, F4, A21)
High IOP	36	35 (D7)
Total	100	95

* Patients D2 and D8 had protocol violations affecting only the right eye and were excluded in the PP analyses submitted in December 2007. Both patients are now included in the PP analyses with the left eye (worse evaluable eye) IOP values.

With regards to the requested extra data (pooled and by subgroup), considered by the CHMP to be of major relevance for assessment of the expected benefit in the target population, the MAH were specifically requested to provide efficacy data pooling the two main pivotal studies (overall and by subgroups, i.e. patients with baseline IOP ≥19-24mmHg, and ≥24-32mmHg at 8 AM while on travoprost), ensuring that patients are correctly classified into each category.

The pooled analyses of the two studies were conducted both for the PP and ITT populations.

The MAH agreed with the CHMP that the IOP reductions observed in the high IOP group of patients in both CM-03-06 and CM-03-06E are consistent with those observed in similar populations with the travoprost and timolol combination and that it is supportive of the current application. The results of the pooled analyses are consistent with those of the individual studies, confirming that the IOP reductions are similar between the Timolol 5 mg/ml and Azopt groups and that the efficacy of the two products is consistent with that observed in studies reported previously.

The key submitted data analysis is summarised in the following tables:

Table 12:

Subgroup Efficacy Analysis (worse eye) – Mean IOP (mm Hg) ± S.D.
CM-03-06E – Per Protocol Data Set

TRAVATAN + AZOPT						
N TOTAL	**97**					
VISIT	**Baseline**		**Week 12**		**IOP Reduction from Baseline**	
Baseline IOP (mmHg) Range	**Low (19-23)**	**High (24-36)**	**Low (19-23)**	**High (24-36)**	**Low (19-23)**	**High (24-36)**
N	69	28	69	28	69	28
8 AM	21.1 ± 1.4	25.6 ± 1.8	17.9 ± 2.7	22.0 ± 2.7	3.2 ± 2.5	3.6 ± 3.4
12 Noon	20.1 ± 2.1	23.4 ± 2.2	16.7 ± 2.4	19.7 ± 2.4	3.4 ± 2.5	3.7 ± 2.7
4 PM	20.1 ± 2.0	22.4 ± 2.9	16.5 ± 2.6	19.8 ± 2.7	3.6 ± 2.5	2.6 ± 2.7
Diurnal	20.4 ± 1.5	23.8 ± 1.7	17.0 ± 2.2	20.5 ± 2.2	3.4 ± 2.0	3.3 ± 2.1
TRAVATAN + Timolol 5 mg/ml						
N TOTAL	**95**					
VISIT	**Baseline**		**Week 12**		**IOP Reduction from Baseline**	
Baseline IOP (mmHg) Range	**Low (19-23)**	**High (24-36)**	**Low (19-23)**	**High (24-36)**	**Low (19-23)**	**High (24-36)**
N	60	35	60	35	60	35
8 AM	21.0 ± 1.4	25.7 ± 1.8	17.7 ± 2.6	21.4 ± 3.9	3.3 ± 2.9	4.3 ± 3.2
12 Noon	19.5 ± 2.0	22.9 ± 2.8	16.7 ± 2.5	19.3 ± 3.8	2.8 ± 2.6	3.6 ± 3.2
4 PM	19.0 ± 2.0	22.0 ± 3.2	16.8 ± 3.0	18.7 ± 3.6	2.2 ± 2.9	3.3 ± 3.3
Diurnal	19.8 ± 1.4	23.5 ± 2.2	17.0 ± 2.3	19.8 ± 3.4	2.8 ± 2.3	3.7 ± 2.4

Table 13:

Subgroup Efficacy Analysis (worse eye) – P values (T-test)
CM-03-06E – Per Protocol Data Set

	P-Values					
VISIT	**Baseline**		**Week 12**		**IOP Reduction from Baseline**	
Baseline IOP (mmHg) Range	**Low (19-23)**	**High (24-36)**	**Low (19-23)**	**High (24-36)**	**Low (19-23)**	**High (24-36)**
8 AM	0.508	0.865	0.622	0.472	0.883	0.397
12 Noon	0.083	0.378	0.837	0.579	0.231	0.882
4 PM	0.004	0.564	0.594	0.161	0.006	0.364
Diurnal	0.015	0.539	0.958	0.312	0.116	0.458

Table 14:
Subgroup Efficacy Analysis (worse eye) – Mean IOP (mm Hg) ± S.D.
Pooled Data – Per Protocol Data Set
New data not submitted in December 2007 response to RfSI

TRAVATAN + AZOPT						
N TOTAL	187					
VISIT	Baseline		Week 12		IOP Reduction from Baseline	
Baseline IOP (mmHg) Range	Low (19-23)	High (24-36)	Low (19-23)	High (24-36)	Low (19-23)	High (24-36)
N	145	42	145	42	145	42
8 AM	21.2 ± 1.3	25.6 ± 1.8	17.9 ± 2.5	21.5 ± 3.1	3.3 ± 2.4	4.1 ± 3.8
12 Noon	20.4 ± 2.2	23.6 ± 2.4	17.2 ± 2.5	19.7 ± 2.7	3.2 ± 2.6	3.9 ± 3.0
4 PM	19.8 ± 2.3	22.5 ± 3.1	16.7 ± 2.5	19.7 ± 3.0	3.1 ± 2.5	2.8 ± 3.2
Diurnal	20.5 ± 1.6	23.9 ± 1.8	17.3 ± 2.3	20.3 ± 2.7	3.2 ± 2.1	3.6 ± 2.6
TRAVATAN + Timolol 5 mg/ml						
N TOTAL	185					
VISIT	Baseline		Week 12		IOP Reduction from Baseline	
Baseline IOP (mmHg) Range	Low (19-23)	High (24-36)	Low (19-23)	High (24-36)	Low (19-23)	High (24-36)
N	129	56	129	56	129	56
8 AM	21.1 ± 1.4	25.7 ± 2.0	17.2 ± 2.8	20.9 ± 4.0	3.9 ± 3.0	4.8 ± 3.4
12 Noon	20.0 ± 2.1	22.9 ± 2.7	16.5 ± 2.7	19.2 ± 4.1	3.5 ± 2.8	3.7 ± 4.0
4 PM	19.3 ± 2.2	22.1 ± 3.0	16.2 ± 2.9	18.6 ± 3.6	3.1 ± 2.8	3.6 ± 3.2
Diurnal	20.1 ± 1.6	23.6 ± 2.1	16.7 ± 2.5	19.6 ± 3.5	3.5 ± 2.5	4.0 ± 2.9

Table 15:
Subgroup Efficacy Analysis (worse eye) – P values (T-test)
Pooled Data – Per Protocol Data Set
New data not submitted in December 2007 response to RfSI

	P-Values					
VISIT	Baseline		Week 12		IOP Reduction from Baseline	
Baseline IOP (mmHg) Range	Low (19-23)	High (24-36)	Low (19-23)	High (24-36)	Low (19-23)	High (24-36)
8 AM	0.6729	0.7516	0.0260	0.3960	0.0470	0.2980
12 Noon	0.1308	0.2163	0.0361	0.5141	0.4093	0.8159
4 PM	0.0611	0.6060	0.1316	0.1015	0.9484	0.2204
Diurnal	0.0904	0.4886	0.0321	0.2541	0.2850	0.4114

Table 16:
Responder Analysis - N and % of patients with IOP ≤ 20 mmHg and P values
CM-03-06 Per Protocol Population

	Week 12									
VISIT	AZOPT				Timolol 5 mg/ml					
	90				90					
Baseline IOP (mmHg) Range	Low (19-23)		High (24-36)		Low (19-23)		High (24-36)		Low (19-23)	High (24-36)
	76		14		69		21			
	N	%	N	%	N	%	N	%	P-values	
8 AM	66	87	8	57	67	97	11	52	0.025	0.782
12 Noon	69	91	9	64	64	93	15	71	0.668	0.656
4 PM	73	96	9	64	66	96	16	76	0.904	0.445
Diurnal	71	93	8	57	65	94	15	71	0.904	0.383

Table 17:
Responder Analysis - N and % of patients with IOP ≤ 20 mmHg and P values
CM-03-06E Per Protocol Population
Revised data from that submitted in December 2007 response to RfSI

	Week 12									
VISIT	AZOPT				TIMOLOL					
	97				95					
Baseline IOP (mmHg) Range	Low (19-23)		High (24-36)		Low (19-23)		High (24-36)		Low (19-23)	High (24-36)
	69		28		60		35			
	N	%	N	%	N	%	N	%	P-values	
8 AM	60	87.0	7	25.0	52	86.7	14	40.0	0.961	0.210
12 Noon	65	94.2	15	53.6	55	91.7	23	65.7	0.573	0.328
4 PM	63	91.3	17	60.7	52	86.7	28	80.0	0.398	0.092
Diurnal	65	94.2	14	50.0	54	90.0	21	60.0	0.373	0.427

Validity of definition for ITT and PP
The definition of the 'per protocol' (PP) population identified an ITT rather than a real PP population, were also questioned by the CHMP, in terms of their acceptability for the primary analysis in a non-inferiority hypothesis trial. Therefore, the MAH was also requested to provide the efficacy results for the ITT and for the PP populations, using generally accepted definitions to identify these populations.

The MAH discussed therefore the validity of their definition for the ITT and PP populations. The new data submitted by the MAH are summarised in the table below:

Table 18
Mean IOP (mmHg) ± S.D. and P-values
CM-03-06E - Revised Per Protocol Analysis

	AZOPT			TIMOLOL			P-Value		
N TOTAL	98			98					
Visit	Mean IOP at Baseline	Mean IOP at Week 12	IOP Reduction from Baseline	Mean IOP at Baseline	Mean IOP at Week 12	IOP Reduction from Baseline	Mean IOP at Baseline	Mean IOP at Week 12	IOP Reduction from Baseline
8 AM	21.6 ± 2.2	18.4 ± 4.1	3.2 ± 4.0	21.8 ± 2.7	18.2 ± 4.3	3.6 ± 3.6	0.6	0.7	0.5
12 Noon	20.6 ± 2.2	16.9 ± 3.6	3.6 ± 3.6	20.1 ± 2.7	17.0 ± 3.8	3.1 ± 3.3	0.2	0.9	0.3
4 PM	20.4 ± 2.3	16.9 ± 3.8	2.9 ± 3.5	19.6 ± 2.7	16.7 ± 3.9	2.3 ± 3.2	0.04	0.7	0.2
Diurnal	20.9 ± 1.9	17.4 ± 3.6	3.4 ± 3.4	20.5 ± 2.4	17.3 ± 3.8	3.2 ± 3.1	0.3	0.8	0.6

The Per Protocol (PP) population analysed in the pivotal study CM-03-06E was revised, to include 196 patients instead of 201. In pivotal study CM-03-06, both the intent-to-treat (ITT) and the PP data sets were selected based on generally accepted definitions. The CHMP considered that the MAH had convincingly addressed this concern, which was thus resolved.

Analysis of non responders
An analysis of responders according to different stringent criteria was also considered to be needed by the CHMP to assess the clinical relevance of the observed effect (e.g. the proportion of patients who achieved an IOP ≤ 20mmHg at week 12 considering different degrees of severities at baseline).

The data submitted by the MAH are summarised in the table below:

Table 19
Responder Analysis - N and % of patients with IOP ≤ 20 mmHg and P-Values
CM-03-06 – Per Protocol

	AZOPT				TIMOLOL				P-value	
N TOTAL	90				90					
VISIT	Week 12				Week 12					
Baseline IOP (mmHg) Range	Low (19-24)		High (24-36)		Low (19-24)		High (24-36)		Low (19-24)	High (24-36)
N	76		14		69		21			
	N	%	N	%	N	%	N	%		
8 AM	66	87	8	57	67	97	11	52	0.025	0.782
12 Noon	69	91	9	64	64	93	15	71	0.668	0.656
4 PM	73	96	9	64	66	96	16	76	0.904	0.445
Diurnal	71	93	8	57	65	94	15	71	0.904	0.383

Table 20
Responder Analysis - N and % of patients with IOP ≤ 20 mmHg and P-Values
CM-03-06E – Per Protocol

	AZOPT				TIMOLOL				P-Value	
N TOTAL	98				98					
VISIT	Week 12				Week 12					
Baseline IOP (mmHg) Range	Low (19-24)		High (24-36)		Low (19-24)		High (24-36)		Low (19-24)	High (24-36)
N	70		28		72		26			
	N	%	N	%	N	%	N	%		
8 AM	62	89	9	32	64	89	10	38	0.95	0.6
12 Noon	67	96	19	68	68	94	17	65	0.7	0.8
4 PM	64	91	21	75	69	96	18	69	0.3	0.6
Diurnal	63	90	16	57	67	93	15	58	0.5	0.96

The information provided did not show major differences among treatment groups. Results consistent with previous treatment combinations of IOP-lowering medications were noted in the subgroup of "high IOP" population (although data are limited to provide definite conclusions). This issue was, however, considered by the CHMP to have been addressed satisfactorily.

In conclusion, all the issues around Efficacy identified by the CHMP during this procedure have been satisfactorily addressed by the MAH.

2.3 Clinical safety

Patient exposure
This summary of safety is based upon 466 patients with exposure to the adjunctive use of a prostaglandin analogue (either travoprost 40 mcg/ml or latanoprost 50 mcg/ml) and a topical carbonic anhydrase inhibitor (Azopt).

Table 21
Number of Patients with Exposure to the Concomitant Use of a Prostaglandin Analogue and AZOPT

Source	Patients with Exposure to the Concomitant Use of a Prostaglandin Analgoue and AZOPT
Controlled Clinical Trials	
CM-03-06	96 (travoprost + brinzolamide)
UK-AL03016	82 (travoprost + brinzolamide)
CM-03-06E	97 (travoprost + brinzolamide)
Subtotal	**275**
Published Literature	
Feldman et al., 2007	84 (travoprost + brinzolamide)
Martinez-de-la-Casa et al., 2004	22 (travoprost + brinzolamide)
Shoji et al., 2005	14 (latanoprost + brinzolamide)
Tsukamoto et al., 2005a	30 (latanoprost + timolol + brinzolamide)
Tsukamoto et al., 2005	25 (latanoprost + timolol + brinzolamide)
Reis et al., 2006	16 (travoprost + brinzolamide)
Subtotal	**191**
OVERALL TOTAL	**466**

Adverse events

Safety Summary for Study CM-03-06:
The evaluation of safety was performed on 189 adult and elderly patients diagnosed with primary open-angle glaucoma or ocular hypertension. All randomised patients were treated with travoprost 40 mcg/ml monotherapy for 4 weeks before they were randomised (96 patients were randomised to brinzolamide 10 mg/ml and 93 patients were randomised to timolol maleate 5 mg/ml).

No safety issues or clinically relevant treatment group differences were observed based upon an evaluation of adverse events and assessment of ocular parameters which included visual acuity (best-corrected Snellen) and ocular signs (lid, anterior chamber, conjunctiva, cornea, lens, vitreous, iris, flare, and cells). No patient deaths or serious adverse events were reported during the study.

The most frequent adverse drug reaction (treatment-related adverse event) reported during either phase of the study was hyperaemia of the eye (either conjunctival or ocular) occurring in 9 patients overall. Overall, all adverse drug reactions reported in patients during either the non-randomised (travoprost 40 mcg/ml once-daily) or the randomised phase of the study (the addition of brinzolamide 10 mg/ml twice-daily) had been previously reported in clinical trials involving either travoprost 40 mcg/ml or brinzolamide 10 mg/ml and are listed in the respective SPCs.

Safety Summary for Study CM-03-06E:
The evaluation of safety was performed on 192 adult and elderly patients who received at least 1 dose of study medication during the non-randomised phase (patients received travoprost 40 mcg/ml once-daily for 4 weeks) and randomised phase (patients received in addition to travoprost 40 mcg/ml once-daily either brinzolamide 10 mg/ml twice-daily or timolol maleate 5 mg/ml twice-daily for 12 weeks) of the study. Ninety-seven patients were randomised to brinzolamide 10 mg/ml and 95 patients were randomised to timolol maleate 5 mg/ml.

No safety issues or clinically relevant treatment group differences were observed based upon evaluation of adverse events and assessment of ocular parameters which included visual acuity (best-corrected Snellen) and ocular signs (lid, anterior chamber, conjunctiva, cornea, lens, vitreous, iris, flare, and cells). No deaths were reported during the study. Three patients reported serious adverse events that were assessed as unrelated to the use of study medication.

The most frequent adverse drug reactions (treatment-related adverse event) reported during either phase of the study were conjunctival hyperaemia occurring in 14 patients and ocular irritation occurring in 9 patients. Conjunctival hyperaemia and ocular irritation are not unexpected events with the use of either a topical prostaglandin analogue or carbonic anhydrase inhibitor and do not represent a safety issue for either medicinal product. Overall, all reported adverse drug reactions (treatment-related adverse events) had been previously observed in clinical trials and are listed in the SPCs for both Azopt and timolol maleate 5 mg/ml.

Safety Summary for Study UK-AL03016:
The evaluation of safety was performed on 82 adult and elderly patients diagnosed with either open-angle glaucoma or ocular hypertension who received at least 1 dose of study drug, which included the concomitant use of Travatan (travoprost 40 mcg/ml eye drops, solution) once-daily + Azopt (brinzolamide 10 mg/ml eye drops, suspension) twice-daily. No deaths were reported during the study.

The most frequent adverse drug reactions (treatment-related adverse events) reported during the study were ocular hyperaemia, occurring in 8 patients, and dysguesia, occurring in 6 patients. Ocular hyperaemia is a known side effect of Travatan and dysguesia is a known side effect of Azopt and neither event represents a safety issue for either study medication. Overall, all adverse drug reactions (treatment-related adverse events) reported in patients with concomitant use of Travatan once-daily + Azopt twice-daily were consistent with the information presented in Section 4.8 of the Summary of Product Characteristics for each medicinal product administered individually. There was no additive or synergistic increase in adverse events observed when the 2 medicinal products were administered concomitantly.

CHMP assessment of Safety Data

A review of safety data from the 3 completed clinical trials revealed no new safety issues in a population of 275 adult and elderly patients with open-angle glaucoma or ocular hypertension administered either Travatan (travoprost 40 mcg/ml) once-daily as monotherapy for 4 weeks and/or Travatan once-daily + Azopt (brinzolamide 10 mg/ml) twice-daily for 12 weeks based upon a review of adverse events and assessment of ocular parameters which included visual acuity (best-corrected Snellen) and ocular signs (lid, anterior chamber, conjunctiva, cornea, lens, vitreous, iris, flare and cells).

The adverse drug reaction profile observed in patients with concomitant use of Travatan once-daily + Azopt twice-daily appears consistent with previous clinical trial experience with the individual components. However, the CHMP considered that, across studies CM-03-06 and CM-03-06E, there was an overall higher incidence of ocular AEs in the brinzolamide/travoprost groups compared with the group with timolol as adjunctive therapy. This was to a large extent due to non-serious increases in conjunctival and eye lid hyperaemia, ocular burning and other signs of local irritation/intolerance. There were also more cases, judged probably or possibly related to treatment, with a decreased vision in the brinzolamide groups (4 cases) than in the timolol-groups (2 cases) plus one additional case in the brinzolamide-group not considered related to treatment.

Even though in general this treatment combinations appears well tolerated, data as provided (i.e. raw data and separately for each study) do not allow concluding on possible changes in the incidence of the expected ADRs when combining both drugs. Therefore, the MAH was requested to provide tabulated pooled data with the overall incidence of those adverse events reported in clinical trials.

Tabulated pooled data
As requested, the MAH provided tabulated pooled data with the overall incidence of those adverse events reported in clinical trials. These data are summarised in table 22 below, presenting the frequency and incidence of adverse drug reactions (treatment-related adverse events) for the adjunctive use of Travatan and Azopt integrated across the 3 clinical trials (CM-03-06, CM-03-06E, and UK-AL03016).

Table 22
Frequency and Incidence of Adverse Drug Reactions in the Randomized Phase – TRAVATAN + AZOPT (CM-03-06, CM-03-06E, UK-AL03016)

Coded Adverse Event Presented by MedDRA System Organ Class and Preferred Term (Version 8.0)	Integrated TRAVATAN + AZOPT N = 275		CM-03-06E TRAVATAN + AZOPT N = 97		CM-03-06 TRAVATAN + AZOPT N = 96		UK-AL03016 TRAVATAN + AZOPT N = 82	
EYE DISORDERS	N	%	N	%	N	%	N	%
Conjunctival hyperaemia	14	5.1	10	10.3	4	4.2		
Eye irritation	13	4.7	9	9.3	1	1.0	3	3.7
Ocular hyperaemia	10	3.6			2	2.1	8	9.8
Growth of eyelashes	7	2.5	6	6.2			1	1.2
Eye pain	5	1.8					5	6.1
Eyelash discolouration	4	1.5	4	4.1				
Visual acuity reduced	4	1.5	3	3.1	1	1.0		
Conjunctival disorder NOS (i.e., conj follicles)	3	1.1			3	3.1		
Foreign body sensation in eyes	3	1.1	3	3.1				
Vision blurred	3	1.1					3	3.7
Dry eye	1	0.4			1	1.0		
Erythema of eyelid	1	0.4			1	1.0		
Eye inflammation	1	0.4					1	1.2
Eyelid oedema	1	0.4	1	1.0				
Keratoconjunctivitis sicca	1	0.4					1	1.2
NERVOUS SYSTEM DISORDERS								
Dysgeusia			7	2.5			6	7.3
Headache			2	0.7			2	2.4
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
Asthma	2	0.7			2	2.4		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
Pruritus	2	0.7	2	2.1				

These data allowed concluding that the safety profile of this combination is the one expected from its individual components. No new safety concerns had arisen. The CHMP considered this issue to have been resolved.

Long-term data
A further issue of concern for the CHMP was the fact that the MAH did not submit long-term data with the combination of brinzolamide and a prostaglandin analogue. Data in analogy with the 6-month data from study C-97-27 with timolol as adjunctive therapy to brinzolamide that was available at the time of approval of Azopt was therefore requested to be provided.

The MAH argued that the proposed new indication was merely an acknowledgment of current clinical practice, where topical carbonic anhydrase inhibitors are commonly used as adjunctive therapy to prostaglandin analogues. Even though this clinical use can not be accepted as the only basis to support a new indication, the CHMP acknowledged that the extensive use of the combination and the lack of safety concerns identified added further reassurance to the data provided. These data show no new safety concerns and lack of additive or synergistic increase in the currently known adverse event profile of each of the individual components. Although these data are limited to 12 weeks, new safety concerns derived from a possible interaction would not be expected. Therefore, although no long-term safety data were provided, the long-term safety profile of this combination was not considered to be an issue, and the CHMP considered this concern to have been addressed.

Cases of decreased vision
During the initial assessment of data submitted with this variation application, the CHMP noted that, across studies CM-03-06 and CM-03-06E, there was an overall higher incidence of ocular AEs in the brinzolamide/travoprost groups compared with the group with timolol as adjunctive therapy. This was to a large extent due to non-serious increases in conjunctival and eye lid hyperaemia, ocular burning

and other signs of local irritation/intolerance. There were also more cases, judged probably or possibly related to treatment, with a decreased vision in the brinzolamide groups (4 cases) than in the timolol-groups (2 cases) plus one additional case in the brinzolamide-group not considered related to treatment. The MAH was therefore requested to discuss and clarify these cases.

In their response, the MAH acknowledged that while both travoprost and brinzolamide offer good ocular safety profiles when used as single therapies, patients treated with these medicinal products in Alcon's Phase III clinical trials, generally exhibited a slightly higher incidence of mild ocular adverse events when compared to patients with exposure to Timolol. Even though the individual characteristics (i.e., intensity, duration, outcome) of the these ocular adverse events were not documented within the 3 clinical study reports, none were serious and there was no clinically relevant difference in the rate of discontinuation comparing treatment groups due to adverse drug reactions. Furthermore, it was noted by the MAH that these adverse events were consistent with the types of events and frequency ranges presented in each product's current SPC and, in the opinion of the MAH, do not represent an untoward safety issue.

Adverse events associated with decreased vision had been reported previously in association with the use of Azopt Eye Drops and other suspension formulations. These events were generally transient or mild, and did not lead to treatment discontinuation, therefore not representing an untoward safety issue. The CHMP considered this issue to have been resolved.

Summary of Safety from Published Literature
Overall, a review of the presented publications revealed no safety issues in a population of adult and elderly patients diagnosed with open-angle glaucoma or ocular hypertension administered a prostaglandin analogue (travoprost 40 mcg/ml or latanoprost 50 mcg/ml), a topical carbonic anhydrase inhibitor (brinzolamide 10 mg/ml or dorzolamide 20 mg/ml), and timolol 5 mg/ml as monotherapy or concomitant therapy.

No serious adverse events were reported in these articles. Adverse drug reactions reported in the articles were of the type previously observed in clinical trials involving both prostaglandin analogues and carbonic anhydrase inhibitors, as presented in Section 4.8 of the SPCs for each of the respective study medications.

In conclusion, all the safety issues identified by the CHMP during this procedure have been satisfactorily addressed by the MAH.

2.4 Pharmacovigilance

Pharmacovigilance system

The MAH provided documents that updated the Detailed Description of the Pharmacovigilance System (DDPS). A statement signed by the qualified person for pharmacovigilance, indicating that the MAH has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the EU or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfilled the legislative requirements.

Risk Management Plan

The MAH submitted a Risk Management Plan (RMP).

Table 23 Summary Of The Eu-Risk Minimisation Plan

Safety	**Proposed pharmaco-vigilance activities**	**Proposed risk minimization activities**
Corneal endothelial decomp-ensation	Routine pharmacovigilance No additional activity is proposed at this time	Routine risk minimization The SPC is up to date. Section 4.4, Special warnings and special precautions for use states: "The possible role of brinzolamide on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count). Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for the cornea. Likewise, in other cases of compromised corneas such as patients with diabetes mellitus, careful monitoring is recommended."
Metabolic acidosis	As above	Routine risk minimization The SPC is up to date. Section 4.2, Posology and method of administration states: "AZOPT has not been studied in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients with hyperchloraemic acidosis. Since brinzolamide and its main metabolite are excreted predominantly by the kidney, AZOPT is therefore contra-indicated in such patients." Section 4.3, Contraindications includes: "Hyperchloraemic acidosis" Section 4.4, Special warnings and special precautions for use states: "AZOPT is a sulphonamide inhibitor of carbonic anhydrase and, although administered topically, is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. Brinzolamide has not been studied in pre-term infants (less than 36 weeks gestational age) or those less than 1 week of age. Patients with significant renal tubular immaturity or abnormalities should only receive brinzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis."
Cardio-vascular disorders	As above	None

The CHMP, having considered the data submitted with the application, is of the opinion that no additional risk minimisation activities are necessary for the safe and effective use of the medicinal product. Azopt is a medicinal product with a well-known safety profile and wide experience of use. The RMP was acceptable to the CHMP.

3. Changes to the Product Information

In addition to the above-described concerns, a number of other aspects relating to the SPC wording proposed by the MAH were identified as issues by the CHMP during this procedure.

In summary, the main areas of concern were the following:

1. In section 4.4, it had to be clearly stated that no long-term data on the combination were available.

2. A condensed summary of the presented clinical trials had to be given in section 5.1, where the following wording was recommended for insertion before the 'paediatric' section:

"*The IOP-reducing effect of Azopt as adjunctive therapy to the prostaglandin analogue travoprost studied. Following a 4 week run-in with travoprost, patients with an IOP ≥19mmHg were randomized to receive added treatment with brinzolamide or timolol. An additional decrease in mean diurnal IOP of 3.2-3.4 for the brinzolamide group and 3.2 to 4.2 mmHg for the timolol group were observed ~~without any significant differences between the treatment groups~~. There was an overall higher incidence of non-serious ocular adverse events, mainly related to signs of local irritation, in the brinzolamide/travoprost groups. The events were mild and did not affect the overall discontinuation rates in the studies (see section 4.8)*"

Deletion of the highlighted text was recommended as, from a statistical and methodological perspective, it conveyed no information on equivalence. Moreover, this information appears in the sentence before were the effect size is described.

Appropriate cross-referencing to any other relevant SPC sections had to be made.

The MAH submitted revised product information, in accordance with the requests from the CHMP.

Conclusions and Benefit / Risk Assessment

The application to extend the indication for Azopt (brinzolamide) to allow the use of azopt as adjunctive to prostaglandin analogues in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension was evaluated by the CHMP.

Results did not show statistically significant differences among treatment groups. However, in order to estimate the possible benefit of this combination in the subgroup of patients for whom other treatment combinations have shown benefit, the MAH provided additional relevant information, i.e. pooled (and by subgroup) efficacy data and further data to clarify some safety aspects.

This additional data provided allow concluding that the expected mean IOP reduction at 8 AM following the addition of Azopt or Timolol to patients with insufficient IOP control (defined as IOP 24-36mmHg) while on Travatan would be 4.1 (3.8) mmHg and 4.8 (3.4), respectively.

These data confirm an additive effect of Azopt when added to patients with insufficient IOP control while on travoprost that is non-inferior to that of timolol added to travoprost, with an acceptable safety profile.

4. CONCLUSION

On 24 April 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.