European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/CHMP/643354/2008

ASSESSMENT REPORT

FOR

AZARGA

International Nonproprietary Name: brinzolamide/timolol

Procedure No. EMEA/H/C/000960

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Alcon Laboratories (UK) Ltd. submitted on 3 December 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for AZARGA, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 24 January 2007.

The legal basis for this application refers to:

A - Centralised / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:
Rapporteur: **Steffen Thirstrup** Co-Rapporteur: **Gonzalo Calvo Rojas**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 3 December 2007.
- The procedure started on 26 December 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2008.
- During the meeting on 21-24 April 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 April 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 8 July 2008.
- During the CHMP meeting on 21-24 July 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 27 August 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 8 September 2008.
- During the meeting on 22-25 September 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to AZARGA on 25 September 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 September 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Primary open-angle glaucoma (poag)
Primary open-angle glaucoma is a chronic, generally bilateral but often asymmetrical disease characterised by a multifactorial optic neuropathy where there is a characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve. There is an evidence of progressive optic nerve damage observed by either or both of the following:

• The presence of the following in the ***optic disc or retinal nerve fibre layer***: 1) diffuse or focal narrowing or notching of the disc rim, especially at the inferior or superior poles; 2) diffuse or localized abnormalities of the retinal nerve fibre layer, especially at the inferior or superior poles; 3) nerve fibre layer haemorrhages; 4) asymmetrical appearance of the optic disc rim in the fellow eye that suggests loss of neural tissue.

• The presence of one or more of the following abnormalities in ***the visual field*** in the absence of other explanations for a field defect: nasal step or scotoma; inferior or superior arcuate scotoma; paracentral scotoma; generalized depression; persistent worsening of the correct pattern standard deviation (CPSD) or corrected loss variance (CLV) on automated threshold perimetry.

The aetiology is multifactorial and the elevated IOP is an important risk factor among several others, e.g. inheritance, age, race, myopia and cardiovascular disease. In the European population above the age of 40 years the occurrence is about 1 %, (accelerating with increasing age).

Other characteristics are:
1. Adult onset
2. Open, normal-appearing anterior-chamber angles
3. Absence of known other (e.g., secondary) explanations for progressive glaucomatous optic nerve change (e.g., pigment dispersion, pseudoexfoliation, iridocorneal endothelial syndrome).

Secondary open angle glaucoma
Characterised by open angles and secondary explanations for progressive glaucomatous optic nerve change due to elevated intraocular pressures caused by e.g. pigment dispersion, pseudoexfoliation, iridocorneal endothelial syndrome or uveitis. The elevated IOP is an important risk factor as in primary open angle glaucoma.

Ocular hypertension
Characterised by a peak IOP>21 mm Hg and <30 mmHg without treatment, with a normal visual field, optic nerve disc, retinal nerve fibre layer and no risk factors.

Management

Open angle glaucomas (primary and secondary)
The purpose of treatment is to enhance the patients´ health and quality of life by preserving visual function without causing untoward effects from therapy. Treatment of the main risk factor, the intraocular pressure, by lowering intraocular pressure (IOP) has until now been the preferred treatment. The treatment aims to maintain the IOP at a pressure below which further optic nerve damage is unlikely to occur in the patient. The IOP can be lowered by medical treatment, laser surgery, and incisional surgery (alone or in combination). The choice of initial therapy depends on numerous considerations, and discussion of treatment should include all appropriate options.

Initial therapy with topical medication
In most instances, topical medications constitute initial therapy. Argon laser trabeculoplasty is an appropriate initial therapeutic alternative and filtering surgery may be an appropriate initial therapy for

some patients with moderate or severe glaucoma. The choice of treatment will have as its goal the greatest potential benefit in light of the level of risk, cost, and alterations in quality of life acceptable to each individual patient.

Medical agents that increase aqueous outflow include topical miotics, topical adrenergic derivatives, and prostaglandin analogues. Agents that decrease aqueous production include carbonic anhydrase inhibitors, alpha$_2$-adrenergic agonists and beta-adrenergic antagonists. To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP. When starting a new topical agent, it is often useful to begin by treating only one eye and comparing the relative change of the IOP in the two eyes at follow-up visits.

Establishing an effective regimen requires attention to its efficacy (potential impact on the disease); toxicity (the drug-induced side effects); and the degree to which efficacy is reduced by non-compliance due to visual, physical, social, economic, or psychologic factors. The ophthalmologist should evaluate each of these issues and choose a regimen of maximal effectiveness with the least medication to achieve the desired therapeutic response for each patient. The goal should as well be to minimize the side effects of management and their impact on the patients´ vision, general health, and quality of life.

The choice of therapy must take into account quality of life, cost and compliance. In many patients beta-blockers have been used as the first line of therapy and first choice since they are effective and usually topically well tolerated; caution must be exercised if the patient suffers from a systemic condition such as bronchopulmonary disease or cardiac arrhythmia, since the systemic absorption of these drugs may cause relevant adverse systemic effects.

Over the past few years there has been a gradual shift in the choice of first time medical therapy. *Prostaglandin derivatives/prostamides (such as latanoprost, travoprost and bimatoprost)* have, in the hands of many ophthalmologists superseded beta-blockers as the first choice, especially after the approval by the FDA in the US and EMEA in Europe as 1st line treatment. The Prostaglandin derivatives/prostamides have gained widespread use due to a high pressure lowering capacity, usually between 25 and 33%, and a high systemic safety profile.

If the first choice alone does not control the glaucoma then the European Glaucoma Society Guidelines recommend to switch or to substitute before using adjunctive therapy in the form of other topical agents. In any individual patient in whom the first choice is not effective and/or tolerated, any of the other topical agents should be initiated as monotherapy. If the target pressure is not reached even after switching then a second medication should be added either as 2 separate bottles or as a fixed combination in one bottle.

Characteristics of fixed drug combinations

Advantages

- Better compliance
- Less toxicity by preservatives

Characteristics of separate drug combinations

Advantages

- Selective dosing and application frequency
- Selective discontinuation due to side effects
- Optimum pharmaceutical preparation oriented to each individual agent

If more than two topical medications or 2 fixed combination bottles are required to control the IOP, then other forms of therapy, such as laser trabeculoplasty or glaucoma surgery, should be considered.

So today, clinicians and patients have a wider range of choices, which generally are associated with fewer adverse effects and require less frequent administration than before. Medical therapy can therefore now be considered as an initial approach to treatment.

About the product

AZARGA eye drops suspension is a fixed combination of two well-known ophthalmic drugs, timolol (5 mg/mL) and brinzolamide (10 mg/mL).

The approved indication for AZARGA is: *Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.*

The recommended dose is *one drop of AZARGA in the affected eye(s) twice daily. AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.*

Brinzolamide is a carbonic anhydrase II (CA-II) inhibitor. These compounds decrease the aqueous humor production by means of inhibiting the conversion of carbon dioxide to bicarbonate in the ciliary body. Inhibition of the carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the production of bicarbonate ions and subsequent reduction in sodium and fluid transport. Oral CAIs such as oral acetazolamide have been a classical treatment for glaucoma, but are very poorly tolerated because of systemic side effects. Adverse events of brinzolamide are mainly local. Most of the systemic side effects of oral carbonic anhydrase inhibitors (CAIs) are not present with topical therapy because they are related to the systemic inhibition of the CA present in many tissues. However, some of the severe side effects, such as blood dyscrasias were not dose-related and therefore, attention should be paid to the occurrence of such side effects. Moreover, brinzolamide is a sulphonamide, which deserves caution, as concerns the potential for hypersensitivity. This is reflected in section 4.4 of the SPC.

Timolol is a non-selective β_1 and β_2 adrenoceptor antagonist that lowers IOP by suppressing aqueous humor formation in humans.

Brinzolamide 1.0% is currently marketed by Alcon for the reduction of elevated IOP under the name Azopt. Brinzolamide was granted a European marketing authorisation via the centralised procedure in 2000 (EMEA/H/C/267) for the decrease of elevated intraocular pressure 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, significantly, as adjunctive therapy to beta-blockers.

Timolol 0.5%, which likewise is indicated in patients with ocular hypertension or open-angle glaucoma for lowering IOP, has been on the market since 1981 in Europe and is generally applied as a 0.5% eye drop solution. It is also available in a 0.25% solution and in a 0.1 mg % gel formulation.

Several prostaglandin analogues + timolol and one carbonic anhydrase inhibitor + timolol fixed combination products have received marketing authorisation in EU Member States through the mutual recognition or centralised procedure, including DuoTrav (EMEA/H/C/665), which is a fixed combination of travoprost 40 µg/ml and timolol 5 mg/ml, authorised on 24 April 2006. As such, AZARGA may be defined as a fixed combination of compounds already approved as co-administration therapy.

No CHMP Scientific Advice was sought, but regulatory advice was obtained from the Spanish Agency (AEMPS) in July 2005 and from the French Agency (AFSSAPS) in September 2005. Questions on quality, non-clinical and clinical issues were discussed.

2.2 Quality aspects

Introduction

AZARGA is presented in the form of eye drops suspension, to be marketed in an opaque, white, low density polyethylene bottle with a natural dispensing plug and white polypropylene closure. The eye drops contain brinzolamide 10mg/ml and timolol 5mg/ml.

The concentration of brinzolamide is the same as in the approved Azopt Eye Drops and the concentration of timolol is the same as in the approved DuoTrav Eye Drops.
Other ingredients are defined in the SPC section 6.1.

Active Substance

***Active Substance:* brinzolamide**

Brinzolamide is an existing drug substance, which has been approved in the EU for use in Azopt eye drops suspension.
The chemical name of brinzolamide is (R)-4-(Ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide The corresponding molecular formula is $C_{12}H_{21}N_3O_5S_3$ and the Relative Molecular Mass 383.51. It is a white to off-white non-hygroscopic powder or crystals odourless or with a faint characteristic odour. The solubility in water is pH dependant with minimal solubility at neutral pH and increased solubility at more basic or acidic pH. Partition coefficient (octanol/water) at pH 5.0 and pH 7.4 are 0.65 and 6.56 respectively. The dissociation constants pK_a are 5.9 and 8.5.
Brinzolamide is optically active. It has a single chiral centre and is produced by stereoselective synthesis process, the configuration established is *R.* Only one crystal form has been observed.

- Manufacture

The synthesis is carried out in 8 adequately described steps. The control methods are described and typical chromatograms are provided where relevant. The process involves the use of one catalyst, lithium-containing reagents and several solvents throughout the process. Suitable specifications of reagents and solvents are provided. The manufacturing process described does not include the use of class 1 solvents, according to the ICH Guideline on Residual Solvents. Reprocessing may take place if necessary.
Six intermediate compounds are isolated in this manufacturing process; sufficient information regarding structural characterization specifications and analytical methods used for the control of each intermediate are provided.
The starting materials that are structurally incorporated into the active pharmaceutical product are commercially available and the current suppliers are provided. Suitable tests and specifications used to control the quality of these starting materials are provided with the exception of sulfur dioxide due to safety considerations in handling of same, the identity test of which is not performed and acceptance is based on a Certificate of Analysis from the vendor.

- Specification

The specifications for the control of brinzolamide includes tests for appearance (visual), identification (IR, chiral HPLC), colour and clarity of solution (PhEur), chiral purity (HPLC), impurities (HPLC), heavy metals (PhEur), loss on drying (PhEur), residual solvents(GC), benzene, residue on ignition (PhEur), assay (HPLC), bioburden (PhEur).
Residual solvents in the drug substance specification are controlled by loss on drying and GC tesing.
Three batches, manufactured according to the optimised procedure, were tested for inorganic impurities that could potentially be present due to the catalyst and the lithium-containing reagents Results were below the detection limit. These batches were screened for additional 44 metals but none was detected.
Batch results for four batches from the proposed manufacturer are provided. These results comply with the proposed specifications.

- Stability

Three pilot scale batches manufactured by the proposed manufacturer using the optimised process have been stored at 25ºC/60% RH for 12 months and at 40ºC/75% RH for 6 months in the proposed market packaging. Parameters investigated: appearance, identity, loss on drying, chromatographic purity and chiral purity. Test methods used are the same as used in the control of the drug substance, except for a TLC method used for identification, which has been adequately described. The applicant committed that the 3 batches of brinzolamide drug substance would continue to be tested for stability using ICH long-term conditions up to 156 weeks.

Stress testing: The influence of heat (50ºC) was studied over 4, 8 and 12 weeks. The sample was stored in the proposed market packaging and no degradation occurred.
A photostability study was also carried out over 28 days. The sample was stored in a capped glass autosampler vial. No significant degradation was observed. The photostability study was performed prior to the ICH guideline. However, with only small differences the study met the requirements of the guideline and therefore the study can be considered valid.
These results indicate that brinzolamide is a stable not photosensitive or hygroscopic drug substance.

Further supportive data were provided from 7 pilot scale batches from a different manufacturer employed during the initial phases of development and 1 batch from the proposed manufacturer. These batches have been studied at 25ºC/60% RH for up to 3 years and at 40ºC/75% RH for up to 6 months in the proposed market packaging.

The overall results support the proposed retest period when stored in the proposed market packaging under the proposed storage conditions.

***Active Substance*: Timolol maleate**

Timolol maleate is described in the European Pharmacopoeia. The corresponding molecular formula is $C_{17}H_{28}N_4O_7S$ and the Relative Molecular Mass 432.49. It is a white or almost white, crystalline powder or colourless crystals. It is soluble in water and in ethanol (96%). The dissociation constant pK_a is 9.2. Timolol maleate is in a crystalline form and no other polymorph forms has been reported or observed. It contains one chiral centre and the form used is the (S)-enantiomer.
With the exception of new batch analysis data the information is the same as that approved in the MA for DuoTrav.

- Manufacture

Regarding the description of manufacturing process and process controls, control of materials, critical steps and intermediates, process validation and manufacturing process development reference is made to the CEP No. R1-CEP 1998-147-Rev 02, which covers all of these aspects.

- Specification

The active substance is controlled according to the requirements of the Ph. Eur. monograph.
Additional requirements for bioburden and related substances are included in the specifications. The residual solvent acetone is controlled by the test for loss on drying. The additional requirements for related substances are as reported in the CEP.
The specifications for the control of timolol maleate includes tests for appearance (visual, thermal), identification (PhEur: IR, TLC, specific optical rotation and visual), appearance and pH of solution (PhEur), enantiomeric purity (PhEur), related substances (PhEur), chromatographic purity (HPLC), heavy metals (PhEur), loss on drying (PhEur), sulphated ash (PhEur), assay (PhEur) and bioburden (PhEur).
Metal catalysts are not used. 5 batches were screened by Alcon and all results were within the specified levels in the guideline for residues of metal catalysts. It is concluded that inorganic impurities are suitably controlled by the sulphated ash test.
Batch results are provided for 4 batches used in the toxicological, clinical and stability studies of the AZARGA eye drops.

- Stability

Stability studies have been evaluated by EDQM and reference is made to R1-CEP 1998-147-Rev 02.
Re-test period and packaging are according to CEP.

Medicinal Product

- Pharmaceutical Development

Only limited formulation development was required because: 1) the concentrations of the actives are the same as in Azopt Eye Drops and DuoTrav Eye Drops; and 2) the selection of the excipients is

based upon those in Azopt Eye Drops. The concentrations of the excipients used in AZARGA are the same as those in Azopt Eye Drops, except for sodium chloride which is slightly reduced to achieve the desired osmolality range. BAC is the antimicrobial preservative agent widely used in topical ophthalmics at this concentration; EDTA is used as a preservative aid.
The formulation used in clinical trials is the same as the one intended for marketing with a minor difference in brinzolamide overage.
A 2% overage of the suspended brinzolamide drug substance is included in AZARGA to compensate for potential losses during manufacturing. Potential loss during manufacturing was documented by batch analysis results for brinzolamide assay in the primary stability batches demonstrating that a 2% overage of brinzolamide is appropriate.
AZARGA is formulated at a pH of approximately 7.2 and is isotonic. Because of brinzolamide's limited solubility at physiologic pH and room temperature, a suspension dosage form was designed. Alcon has further evaluated three key characteristics (particle size, polymorphism and uniformity/ homogeneity of dose) during development. Polymorphism of timolol maleate has been studied, but polymorphism and particle size of timolol maleate is not issues since it is in solution.
Particle size is determined by the milling step applied during manufacture of the finished dosage form. A validated HIAC method is used in the evaluation of particle size distribution. The particle size distribution does not change during stability studies. Experience with other eye drops shows that the proposed specification is well tolerated.
Polymorphism of brinzolamide has been studied extensively and the results strongly indicate that the formation of polymorphs in the suspension is not likely to occur.
Finally, AZARGA has been developed to be a homogeneous suspension which shows minimal sedimentation and is easily resuspendable. The resuspendability has been assessed on the primary stability batches and the product is consistently resuspended within five seconds. The uniformity of dose delivered in one drop has been tested for both drug substances and the uniformity was confirmed. Results on intra- and inter-batch variability in homogeneity confirmed uniformity of content for the two drug substances.
The manufacturing process for AZARGA was chosen to provide an adequate level of sterility assurance while maintaining the safety, efficacy and stability of the product. The procedure selected is based upon the approved manufacturing process for Azopt Eye Drops, with the exception of the separate addition of timolol maleate.
A drop size study was conducted to simulate patient use of AZARGA. An average drop size of 33µl$\pm$2.2 µl was obtained.
The bottles and plugs will be sterilised by gamma irradiation since it is an effective process and is compatible with these packaging components. Closures will be sterilised by exposure to ethylene oxide. Ethylene oxide sterilisation of the closures is needed since a gamma sterilised polypropylene resin which meets Ph. Eur. requirements has not been identified for this packaging configuration. The EtO process is compatible with the closures.
The packaging material has been used for numerous ophthalmic products and does not produce significant levels of extractables/leachables; as indicated by a study carried out to evaluate them. It also provides sufficient photo protection to the light sensitive timolol.
The antimicrobial effectiveness of AZARGA has been determined using an organism challenge approach based on the methods described in Ph.Eur and was validated. Samples exhibited acceptable activity against gram-positive, gram negative, yeast and mold. AZARGA meets Ph.Eur. criteria after 52 weeks of storage at room temperature.
The efficacy of the preservative system has also been proven for a formulation containing the concentrations of the preservative and preservative aids at their lower limit of shelf life specification (80%).
Sterility test results initially and following storage for up to 52 weeks at 25°C for three primary stability lots show that Ph. Eur. 2.6.1. Sterility Test requirements are met by AZARGA Eye Drops.

- Adventitious Agents

None of the excipients used in the drug product are of human or animal origin.

- Manufacture of the Product

The manufacturing process selected is based upon the approved manufacturing process for Azopt, with the exception of the separate addition of timolol maleate. It consists of the following six steps:

1. Preparation of the brinzolamide milling slurry
2. Preparation of carbomer slurry/vehicle concentrate
3. Preparation and addition of timolol maleate
4. Aseptic addition of milling slurry
5. Sterile filling
6. Secondary packaging

The sterilisation method is a combination of steam sterilisation, Gamma sterilisation, Ethylene Oxide sterilisation during the various steps of the manufacturing process. The sterility of the finished product is achieved by employing aseptic techniques and sterile filling at the last steps of the process.
Sterility issues including sterilisation procedures, and aseptic procedures, critical steps and holding times are adequately addressed and justified. The residual content of ethylene oxide and ethylene chlorohydrin will be below the limits specified in the guideline on Limitations to the use of Ethylene Oxide in the Manufacture of Medicinal Products. The milling process and uniformity of the suspension during filling has been justified and documented. The process validation is supported by batch data on 3 production scale batches.

- Product Specification

The specification for batch release and shelf-life include the following tests: brinzolamide identity (TLC/HPLC), brinzolamide assay (HPLC), brinzolamide impurities (HPLC), timolol identity (TLC/HPLC), timolol assay (HPLC), timolol impurities (HPLC), any single unspecified impurity (HPLC), total impurities (HPLC), benzalkonium chloride identity (HPLC), benzalkonium chloride assay (HPLC), disodium edetate identity (HPLC), disodium edetate assay (HPLC), pH (Ph. Eur), osmolality (Ph. Eur), appearance (visual), viscosity (Ph. Eur), redispersibility (mechanical), particle size (HIAC), Sterility (PhEur) and fill volume.
Batch analyses data are reported from three production scale batches. Analytical data of smaller batches used in toxicology and clinical evaluation were also included. The results comply with the specification and confirm consistency of the product.

- Stability of the Product

The first 3 production scale batches of the product have been put on stability and they are tested according to the stability protocol. The three batches have been stored at 25ºC/40% RH for 18 months, at 30°C/65% RH for 18 months and at 40ºC/25% RH for 6 months in the proposed market packaging. The containers were stored in the horizontal position. The applicant committed to continue all ongoing stability studies until protocol completion.

Photostability was part of the stability study on the 3 primary stability batches. Samples were stored in a light cabinet with or without secondary packaging for 6 weeks under specified conditions. Results showed the drug product is sensitive to extreme light condition; however it is not enough to warrant any special storage declaration.

In-use stability: In-use stability was studied on two primary stability batches (at 25˚C/40%RH/12 months) in accordance with the guideline on In-use Stability Testing of Human Medicinal Products. One drop twice per day was dispensed from each bottle for a period of 30 days. Full physical and chemical testing was conducted initially and at the end of the 30 day period. No significant differences were seen from the initial to the 30 day time point.
Four drops per day from each of 10 containers were expelled and at the end of a 30 day period the remaining product was tested for total viable microbial count in accordance with EP. No viable bacteria or fungi were detected.

Discussion on chemical, pharmaceutical and biological aspects

The quality of AZARGA eye drops suspension is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of all the important product quality characteristics. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking dated 22 September 2008 and committed to resolve these as Follow-Up Measures after the opinion, within an agreed timeframe.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

It can be safely concluded that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction

AZARGA is a fixed combination of compounds already approved as co-administration therapy. Moreover, patient exposure to brinzolamide and timolol for AZARGA is approximately the same as for the above-mentioned products. In such cases, there is generally no need for additional non-clinical studies (CPMP/EWP/240/95).

Since Azopt and DuoTrav were developed by the same Applicant, substantial parts of the non-clinical dossier on AZARGA are identical to those that were submitted to and reviewed on behalf of CHMP in the course of the approval of Azopt and DuoTrav in 2000 and 2006, respectively. In addition, the Applicant has conducted new studies addressing the uptake of the active substances from, and the safety of, the proposed fixed combination product following topical application to the eyes of rabbits.

Pharmacology

The fixed combination of brinzolamide and timolol has not been tested in any non-clinical pharmacology studies. This is accepted as the active ingredients are already approved for co-administration therapy.

Pharmacokinetics

All new kinetic studies employed validated methods of analysis using ultraperformance liquid chromatography (UPLC) with ultraviolet (UV) detection for the determination of brinzolamide and an HPLC tandem mass spectrometry method for the determination of timolol.

Systemic absorption of AZARGA was evaluated in the course of a 9-month chronic topical ocular irritation and systemic toxicity study of brinzolamide/timolol eye drops in the rabbit, suspensions following nominal daily doses of 1.6, 2.4 and 4.8 mg brinzolamide and 0.8, 1.2 and 1.2 mg timolol. The maximum mean brinzolamide and timolol concentrations at the end of treatment were 6.84 ± 0.699 µg/ml and 10.7 ± 4.19 ng/ml, respectively. Brinzolamide exposure (C_{max} and AUC_{0-2h}) in whole blood increased from Day 1 to Day 92. Exposure from Day 92 to Day 273 did not change substantially indicating steady-state had been achieved for brinzolamide by Day 92. Timolol exposure (C_{max} and AUC_{0-2h}) was essentially unchanged from Day 1 to Day 273 suggesting that no accumulation occurred and steady-state was achieved.

In a 2-week ocular uptake study in New Zealand White rabbits following topical ocular administration of AZARGA, Azopt or timolol 5 mg/ml Eye Drops, Solution, the AUC_{0-6h} values for brinzolamide in whole blood were significantly different ($p < 0.05$) different for AZARGA at 89% of those found for Azopt, whereas timolol plasma levels were almost double in the group dosed with AZARGA as compared to the group dosed with timolol 5 mg/ml Eye Drops, Solution. The latter finding was not reproduced in humans, however, and is unlikely to be clinically relevant.

In the ocular uptake study referred to above, the AUC_{0-6h} values for brinzolamide in iris-ciliary body were significantly ($p < 0.05$) different for AZARGA at 124% of those found for Azopt, whereas the AUC_{0-6h} values for cornea and aqueous humour and all C_{max} values demonstrated no statistically significant differences. Mean N-desethyl brinzolamide concentrations were below the limits of quantification at all time points for all tissues. Timolol ocular exposures (C_{max} and AUC_{0-6h}) were approximately 3-fold higher for AZARGA as compared to timolol 5 mg/ml, reflecting greater ocular absorption of timolol for the combination. Similar results were observed in a preliminary, non-GLP study.

No new metabolism studies, excretion studies or interaction studies of AZARGA with other medicinal products have been submitted. This is accepted as the active ingredients are already approved for co-administration therapy.

Toxicology

No single-dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity, antigenicity or metabolite studies have been conducted with the fixed combination of brinzolamide and timolol. This is accepted as the active ingredients are already approved for co-administration therapy.

The proposed fixed combination of brinzolamide and timolol was tested in three topical ocular repeat-dose toxicity studies in albino and pigmented rabbits administered 1 drop to each eye up to 3 times a day for up to 9 months of either vehicle, AZARGA, or brinzolamide 20 mg/ml + timolol, 5 mg/ml eye drops, suspension. None of these studies revealed any signs of systemic or ocular toxicity other than a very slight to slight (5-10%) increase in corneal thickness in all dose groups with no relation to dose. A similar increase in corneal thickness was observed in rabbits following 1, 3 and 6 months of treatment with Azopt (brinzolamide eye drops), whereas brinzolamide did not cause significant change in corneal thickness in a 1-year topical ocular study in monkeys.

There are no new impurities or specifications for brinzolamide or timolol relative to those pertaining to Azopt and DuoTrav. Thus, no further studies were performed.

As a rule, photosafety testing is required for drug substances absorbing in the range of 290-700 nm. Since brinzolamide absorbs at 252 nm, no testing was performed. Timolol has peak absorption at maximum wavelengths of 210 nm and 294 nm. Formal photosafety studies have not been performed and are not considered necessary, given the absence of relevant signals in spite of the extensive clinical use of timolol for topical ocular treatment and the marginal trespassing of the 290 nm cut-off.

Based on the estimation of exposure and calculation of the PEC (Predicted Environmental Concentration) AZARGA is unlikely to pose any perceivable risk to the environment.

2.4 Clinical aspects

Introduction

An overview of the main clinical studies conducted with AZARGA is shown below:

Clinical Development Plan for AZARGA

Protocol Type (No.)	Study Design	Subject/Patient Population	Treatment Groups	Dosing Regimen[a]	Dosing Duration	Total No. Randomised: Total No. Exposed to AZARGA
Safety/Efficacy C-97-22	Randomised, double-masked, parallel group	Adults, primary open-angle glaucoma or ocular hypertension	• AZARGA • Timolol	• 1 drop BID • 1 drop BID	2 weeks	66 total: 33 AZARGA
Topical PK C-05-27	Randomised, double-masked, 3 way crossover	Healthy adults	• AZARGA • Azopt • Timolol	• 1 drop BID[b] • 1 drop BID[b] • 1 drop BID[c]	15 weeks (2 weeks oral + 13 weeks topical ocular)	87 total: 26 AZARGA
Comfort C-05-49	Randomised, double-masked, parallel group	Adults, open-angle glaucoma or ocular hypertension	• AZARGA • Cosopt	• 1 drop BID • 1 drop BID	1 week	95[d] total: 48 AZARGA
Pivotal Safety/Efficacy C-05-24	Randomised, double-masked, parallel group	Adults, open-angle glaucoma or ocular hypertension	• AZARGA • Azopt • Timolol	• 1 drop BID • 1 drop BID • 1 drop BID	6 months	523 total: 174 AZARGA
Pivotal Safety/Efficacy C-05-10	Randomised, double-masked, parallel group	Adults, open-angle glaucoma or ocular hypertension	• AZARGA • Cosopt	• 1 drop BID • 1 drop BID	12 months (6 months + 6 months)	437 total: 220 AZARGA
					Total Subject/Patient Exposure	**1203[e] total: 501 AZARGA**

[a] In the affected eye(s)

[b] Oral administration of 1 capsule of brinzolamide 1 mg BID for the first 2 weeks

[c] Oral administration of 1 capsule of Placebo BID for the first 2 weeks

[d] 96 subjects were randomised but 1 never received the study medication

[e] This total only includes topical ocular dosing. Patients in protocol C-05-27 received either brinzolamide 1 mg capsules or placebo capsules before they were randomised to the topical ocular phase. Five patients in C-05-27 were not randomised into the topical ocular phase of the study and are therefore not reflected in the total number of patients. BID = twice daily Timolol = Timolol 5 mg/ml Eye Drops, Solution Cosopt = dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution
AZARGA = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension

GCP

The Clinical trials were performed in accordance with GCP, as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The applicant has performed one comparative study (C-05-27) in healthy volunteers on the PK of the fixed combination product AZARGA as compared to individual products timolol and brinzolamide alone. The aim of the study was to compare the steady state pharmacokinetics of brinzolamide and its primary N-desethyl metabolite in whole blood, and of timolol in plasma following topical administration. The results demonstrate that no differences in Cmax or AUC are seen for brinzolamide or its metabolite comparing the fixed dose combination to brinzolamide alone. For timolol, systemic exposure is about 32% lower when applied as the fixed combination product compared to timolol alone. There is no apparent or plausible explanation for this finding. This is very unlikely to be of clinical relevance. The PK of the fixed combination has not been studied in special populations. Gender differences found for the fixed combination product is of the same order of magnitude as documented for the Azopt formulation and unlikely to be of clinical relevance.

There are no adopted guidelines for PK of fixed combinations of approved medicinal products, but the study performed is adequate and in accordance with suggestions in a draft guideline published at the time of submission.

Pharmacodynamics

Brinzolamide is a potent inhibitor of human carbonic anhydrase II (CA-II). Inhibition of the carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing production of bicarbonate ions and subsequent reduction in sodium and fluid transport.

Timolol maleate is a non-selective beta-adrenergic receptor-blocking agent. When applied topically to the eye, it reduces elevated, as well as normal, intraocular pressure. The exact mechanism of action of this ocular hypotensive action is not clearly established at this time. It is suggested that its predominant action may be related to reducing aqueous humour formation; however, in some studies a slight increase in outflow facility has been observed.

Clinical efficacy

The clinical development plan included 5 clinical trials (see table): a pilot safety/efficacy trial (C-97-22), a pharmacokinetic trial, an ocular comfort trial (C-05-49) and 2 long-term pivotal safety and efficacy trials (Studies C-05-24 and C-05-10). Two further studies were currently ongoing at the time of application. Study C-07-16 compared the effects of AZARGA and Combigan (brimonidine plus timolol) on ocular blood flow and ocular perfusion pressure, and Study C-07-47 evaluates patients preference AZARGA compared to Cosopt (dorzolamide plus timolol) based on ocular comfort.

The initially proposed therapeutic indication for AZARGA was:

Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction or is not well tolerated (see section 5.1*)*

After evaluation of the results of the submitted clinical trials (see discussion below), the indication has been reworded as

"Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction (see section 5.1)"

as it was not the intention of the clinical trials carried out with AZARGA to show a benefit in patients not tolerant to their current IOP medication. Furthermore, patients being treated with monotherapy who are not tolerant to their medication may switch to a different active substance in monotherapy as well before starting a combination product.

Dose response studies

Dosing of AZARGA is based on that of the individual approved, marketed products.
This fixed dose combination contains the two active components, i.e. brinzolamide and timolol maleate and, since they are believed to have different mechanism of action, it is plausible that a combined effect results in additional IOP reduction compared to either compound administered alone. The submitted programme might have included a comparison between the single components administered adjunctively versus the fixed combination. However, the adjunctive use of timolol with brinzolamide is well established. This was based on 4 trials in the original Azopt dossier: C-93-86, C-95-38, C-95-39, and C-97-27, in which the efficacy of the unfixed combination of brinzolamide 10 mg/ml Eye Drops (Azopt) and timolol 5 mg/ml Eye Drops was evaluated.
The results are reflected in the approved therapeutic indication of Azopt: *Azopt is indicated to 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 contraindicated, or as adjunctive therapy to beta-blockers.

Studies conducted with the co-administered products showed efficacy with no increase in the incidence of adverse events reported for the individual components and thus the proposed dosage for the fixed combination appears reasonable and was supported by pivotal studies results.

Main studies

This section of the application summarizes the clinical efficacy data of the 3 studies (C-97-22, C-05-24, and C-05-10) conducted to establish the IOP-lowering efficacy and safety in patients with open-angle glaucoma or ocular hypertension. C-05-24 and C-05-10 are the 2 pivotal studies in this application demonstrating the efficacy of AZARGA, while Study C-97-22 was a pilot study.

Methods

- **Study Participants**

The study population consisted of patients with primary open-angle glaucoma or ocular hypertension.

A summary of the patient demographics (age, gender, race, iris colour, diagnosis) for each of the 4 studies relevant to the evaluation of the efficacy and comfort of AZARGA is provided in the table below:

Patient Demographics
(Intent-to-Treat Data)

		C-97-22	C-05-24	C-05-10	C-05-49	Total
Total No. Patients in ITT Dataset		**66**	**517**	**431**	**95**	**1109**
Race	Caucasian	45	349	314	62	770
	Black	4	91	59	17	171
	Asian	N/A	7	19	1	27
	Hispanic	N/A	66	36	15	117
	Other	17	4	3	0	24
Age	Mean Age (years)	60.8	62.8	64.9	67.6	64.0
	≥18 and <65 years	40	286	195	37	558
	≥ 65 years	26	231	236	58	551
Sex	Male	19	221	180	33	453
	Female	47	296	251	62	656
Eye Colour	Brown	35	287	199	49	570
	Hazel	16	82	42	19	159
	Green	2	19	24	7	52
	Blue	13	121	136	20	290
	Grey	0	8	30	0	38
Diagnosis	Ocular Hypertension	6	189	105	31	331
	Open-Angle Glaucoma	58	311	285	62	716
	Pigmentary Glaucoma	1	10	13	2	26
	Pseudoexfoliation Glaucoma	1	7	27	0	35
	Angle closure Glaucoma	0	0	1	0	1

Overall, these demographics are representative of the population that would be expected to receive this medicinal product.

In order to establish an off-therapy IOP baseline, patients were required to discontinue use of all IOP-lowering medications for a minimum period of 5 days (± 1 day) to 28 days (± 1 day) prior to Eligibility 1 Visit. The duration of washout was based on the duration of action and drug half-life of the medications and was consistent with published studies.

The inclusion/exclusion criteria were chosen to provide similar patient groups across the 2 pivotal efficacy studies, with the exception of the IOP entry criteria and the washout requirements.

- Adult patients of either sex and of any race diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.
- Patients who wore contact lenses were allowed to participate in the study (except in C-97-22 and C-05-49), provided that the contact lenses were removed before instillation of study medication. The patients were instructed to wait 15 minutes following drug instillation before re-inserting their lenses.
- Patients were required to discontinue use of all IOP-lowering medications for a minimum period of 5 days (± 1 day) to 28 days (± 1 day) prior to Eligibility 1 Visit.

The exclusion criteria respected the contraindications for the single components of the study drugs.

Patients less than 18 years of age (21 years of age in C-97-22) were excluded from participation in the clinical trials because elevated IOP in a paediatric population has a different aetiology and is more difficult to treat than in adults.

Prior to study entry, patients were screened and discontinued their anti-glaucoma medication, if any. A wash-out period corresponding to the single anti glaucoma agents had been defined.
The following limits were used: Miotics, systemic and topical CAIs: 5 days; α and α/β- agonists: 14 days; and β-blockers and prostaglandin analogues: 28 days. Thus, baseline IOP values represent off-therapy values, except in Study C-97-22, where patients insufficiently treated on timolol (BID in open label monotherapy) were selected.

Pre-Study IOP-Lowering Medications in AZARGA
Pivotal Studies (C-05-24 and C-05-10)

Number of Medications	All Studies (N=943)		C-05-24 (N=511[b])		C-05-10 (N=432[a])	
	N	%	N	%	N	%
0	127	13.5	125	24.5	2	0.5
1	614	65.1	304	59.5	310	71.8
2	162	17.2	60	11.7	102	23.6
3 or 4	40	4.2	22	4.3	18	4.2

[a] Pre-study medications for 5 patients did not satisfy criteria for inclusion in C-05-10 analysis
[b] Pre-study medications for 12 patients did not satisfy criteria for inclusion in C-05-24 analysis

Pre-Study IOP-Lowering Monotherapy in AZARGA
Pivotal Studies (C-05-24 and C-05-10)

Medication Type	All Studies (N=943)		C-05-24 (N=511[b])		C-05-10 (N=432[a])	
	N	%	N	%	N	%
Beta-Blocker	166	17.6	70	13.7	96	22.2
CAI[c]	41	4.3	15	2.9	26	6.0
Prostaglandin	373	39.6	199	38.9	174	40.3
Alpha-Agonist	32	3.4	19	3.7	13	3.0

[a] Pre-study medications for 5 patients did not satisfy criteria for inclusion in C-05-10 analysis
[b] Pre-study medications for 12 patients did not satisfy criteria for inclusion in C-05-24 analysis
[c] Carbonic anhydrase inhibitor

The IOP to qualify for entry into the efficacy studies is presented below.
Following washout of the previous IOP-lowering medications, patients must have met the following IOP entry criteria in two different visits in at least one treated eye: an upper IOP limit of 36 mmHg, chosen for safety reasons, and a lower limit that varied across studies and ranged from 22 (pilot study) to 24 (pivotal studies) at 8AM. The pilot study required patients to have insufficient control while on timolol treatment to be randomised. Study C-02-24 (contribution of elements) did not require patients to be insufficient responsive to another IOP lowering medication while Study C-05-10 (non-inferiority trial) made some restrictions in this regard: only patients who could benefit from a combination therapy in the investigator's opinion where allowed for study entry.

Qualifying IOP for Studies C-97-22, C-05-24 and C-05-10

Study	Qualifying IOP[a] (mmHg)					
	Eligibility Visit 1			Eligibility Visit 2		
	8 AM	10 AM	4 PM[c]	8 AM	10 AM	4 PM[c]
C-97-22[b]	22 to 36	22 to 36	N.A.	22 to 36	22 to 36	N/A
C-05-24	24 to 36	21 to 36	≤ 36	24 to 36	21 to 36	≤ 36
C-05-10	24 to 36	21 to 36	≤ 36	24 to 36	21 to 36	≤ 36

[a] IOP in the qualifying eye(s) following washout (except in C-97-22). Neither eye could have an IOP > 36 mmHg at any time point or visit
[b] IOP after patients had a minimum 3-week Timolol 5 mg/ml Eye Drops run-in
[c] The same criteria applied to the 12 Noon and 8 PM visits in study C-05-24
N/A = Not applicable

With the exception of the IOP entry criteria and the washout requirements, most inclusion criteria were common across efficacy studies (C-97-22, C-05-24 and C-05-10): Adult patients of either sex and of any race diagnosed with open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension.

- **Objectives**

The therapeutic usefulness of the combination Brinzolamide plus Timolol has been previously demonstrated by means of the studies that supported the concomitant use of both drugs during the MAA for these drugs. The current clinical development programme aimed to support the advantages of a fixed dose combination product and relied on two pivotal studies intended to prove efficacy by means of a contribution of elements study and comparative efficacy/safety against a reference treatment, which followed the recommendations stated in the CPMP/EWP/240/95 Rev. 1 Guideline on fixed combination medicinal products. Overall, studies designs were similar to previous studies performed in open-angle glaucoma or ocular hypertension to support the MAA of different IOP-lowering medications and thus, were considered adequate.

- **Outcomes/endpoints**

Primary endpoint: Mean IOP was the primary efficacy parameter.

Secondary endpoints: The proportion of patients with IOP less than 18 mmHg at selected or all time points was a secondary variable in order to assess clinical relevance of therapy for individual patients in the 2 pivotal studies (C-05-24 and C-05-10). Mean change in IOP and mean percent change in IOP from baseline were used as secondary variables because they are alternate endpoints that take baseline IOP into account.

IOP was measured at least at 2 time points during the day (8 AM and 10 AM) at all study visits for the 2 pivotal efficacy trials (C-05-24 and C-05-10), while further time points (12 Noon, 4 PM and 8 PM) were measured at some of the visits or some of the sites in these studies.

The 4 PM time point represents the latest practical time point in the day at which IOP can be measured in large-scale clinical trials. It represents an 8-hour trough effect for Timolol and Brinzolamide dosed in the morning as single agents or in combination. The 4 PM time point was measured in all patients at key visits in Study C-05-10 (Baseline, Month 6, Month 12) and in Study C-05-24 (Baseline, Month 3, Month 6, at selected sites).
Additionally, at selected sites in Study C-05-24, IOP was measured at 2 further time points, 12 Noon and 8 PM. This allowed an evaluation of the efficacy of AZARGA over an extended diurnal curve.

- **Statistical methods**

If both eyes were dosed, the worse evaluable eye was selected for analysis.

Per protocol data and intent-to-treat results are provided for all efficacy studies. For non-inferiority hypotheses, per protocol data were considered primary, while for superiority hypotheses, intent-to-treat data were considered primary. In all cases, results from both data sets are included to demonstrate robustness of the efficacy findings.

All patients who received study medication and had at least 1 on therapy study visit were considered evaluable for the intent-to-treat analysis. All patients who received study medication, had at least 1 on-therapy study visit and satisfied inclusion/exclusion criteria were considered evaluable for the per protocol analysis. The intent-to-treat data sets include imputed values for all missing data, including those for patients who were early discontinuations if on-therapy data were available. Baseline (pre-randomization) values were not carried forward. No imputation for missing data was performed in the per protocol data sets. Thus comparisons of per protocol and intent-to-treat AZARGA results evaluate the robustness of the result with regard to truncated observations and missing data.

In the long-term pivotal study that tested non-inferiority as the primary statistical objective (C-05-10), a criterion of 1.5 mmHg difference was used.
In the pilot study (C-97-22), only descriptive statistics were provided, based on the intent-to treat data.

- **Design and Results of Individual Studies**

Study C-97-22 Pilot Safety/Efficacy Study
Study C-97-22, conducted in the USA, was designed as a double-masked, parallel trial with 2 treatment groups: AZARGA dosed BID or Timolol 5 mg/ml Eye Drops dosed BID. The study population consisted of patients with primary open-angle glaucoma or ocular hypertension who demonstrated a need for combination therapy. After a minimum 3-week run-in on open-label Timolol 5 mg/ml Eye Drops BID, patients must have had on-therapy IOPs of at least 22 mmHg in at least 1 eye (the same eye) at 8 AM (after 8 PM dosing at with Timolol 5mg/ml Eye Drops) and 10 AM (after 8 AM dosing with Timolol 5 mg/ml Eye Drops) at both Eligibility Visits 1 and 2. The IOP could not be greater than 36 mmHg in either eye at any time point. If these IOP criteria were met, patients were randomized to receive either AZARGA dosed BID or Timolol 5 mg/ml Eye Drops dosed BID. Patients instilled masked medication in both eyes at 8 AM and 8 PM throughout the 2-week Treatment Phase. The treatment Phase consisted of 3 visits (Day 1, Day 7 and Day 14) during which IOP was measured at 5 time points.

Of the 66 enrolled patients (33 on AZARGA and 33 on Timolol 5 mg/ml Eye Drops), all were evaluable for the intent-to-treat analyses (ITT) and 63 (33 on AZARGA and 30 on Timolol 5 mg/ml Eye Drops) were evaluable for the PP analyses. The PP analysis served as the basis for the assessment of efficacy. After a 3-week run-in on open-label Timolol 5 mg/ml Eye Drops dosed BID, mean IOP reductions from baseline across the 5 on-therapy time points ranged from 2.8 to 3.3 mmHg for AZARGA and from 1.4 to 2.4 mmHg for Timolol 5 mg/ml Eye Drops.

All mean IOP reductions from baseline were clinically relevant and statistically significant ($p \leq 0.0005$). Statistically significant differences in mean IOP change from baseline ($p \leq 0.0413$) were observed between the 2 treatment groups at all but the Day 7 10 AM time point (mean reduction in IOP was numerically superior for the AZARGA group 3.3 mmHg versus 2.3 mmHg, $p=0.0679$). Similar results were observed for the intent-to-treat analysis.

Comparison of Mean IOP Change from Baseline (mmHg)
(C-97-22, Per Protocol Data)

	Baseline		Day 1	Day 7		Day 14	
	8AM	10AM	8AM	8AM	10AM	8AM	10AM
AZARGA							
Mean	24.6	23.7	-2.8	-2.7	-3.3	-3.2	-3.3
N	33	33	33	33	33	33	33
Timolol							
Mean	23.9	23.4	-1.6	-1.4	-2.3	-1.7	-2.3
N	30	30	30	28	28	30	30
Difference	0.7	0.3	-1.2	-1.3	-1.0	-1.6	-1.1
P-value	0.1736	0.5965	0.0200	0.0144	0.0679	0.0034	0.0413
Upper 95% CI	1.76	1.32	-0.20	-0.26	0.07	-0.52	-0.04
Lower 95% CI	-0.32	-0.76	-2.28	-2.38	-2.04	-2.60	-2.12

AZARGA = Brinzolamide 10 mg/ml – Timolol 5 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution
*Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.
P-values and confidence intervals were based on repeated measures analysis of variance.

The design of this pilot study was similar to that previously performed with the unfixed combination (Study C-93-86). It is noted that a 3-week run-in on timolol appears limited to achieve the maximum effect, which is substantiated by the additional IOP decrease in the timolol group during the randomised period. Despite that, statistically significant differences over timolol were found, with mean IOP decreases from 2.8 to 3.4 in the AZARGA treatment group as compared to 1.4 to 2.4 in the timolol group.

The magnitude of the observed effect at 2-weeks was, however, slightly lower in both treatment groups to that previously seen (from 3.3 to 4.6 mmHg in timolol+brinzolamide group *vs* from 0.9 to 2.00 mmHg in the timolol group), which might be explained by the fact that patients with lower IOP values at baseline while on timolol were allowed for inclusion. The possible contribution of a lower exposure to timolol in the AZARGA group as compared to timolol monotherapy can not be firmly ruled out.

Despite these considerations, the aim of a pilot study, i.e. a preliminary estimation of the effect with the fixed combination, was reached and the results supported going throughout the established phase III development plan.

Contribution of Elements – Study C-05-24 Pivotal Safety/Efficacy Study

Study C-05-24 was designed to compare the safety and IOP-lowering efficacy of AZARGA (brinzolamide/timolol, fixed combination) to the individual components, i.e. Timolol 5 mg/ml dosed and Azopt dosed twice daily in patients with open-angle glaucoma or ocular hypertension. The study was a multicenter, double-masked, parallel group trial.
The primary outcome was the mean IOP at 8 am and 10 am at week 2, month 3 and month 6 visits. At selected sites (about 25 %) corresponding to approximately 33 % of the enrolled patients, the IOP was also assessed at 12 noon, 4 pm, and 8 pm.
Secondary outcome was the percentage of patients who obtained and maintained < 18 mm Hg through all on-therapy visits.

Following a washout period of the IOP previous medication, 523 patients who met IOP and additional selection criteria were randomly assigned to each of the three treatment groups. Of these, 517 constituted the ITT population. Patients were followed for up to 6 months in a masked way.

Table 10.1.-3:
Disposition of Randomized, Efficacy-Evaluated, and Safety-Evaluated Patients

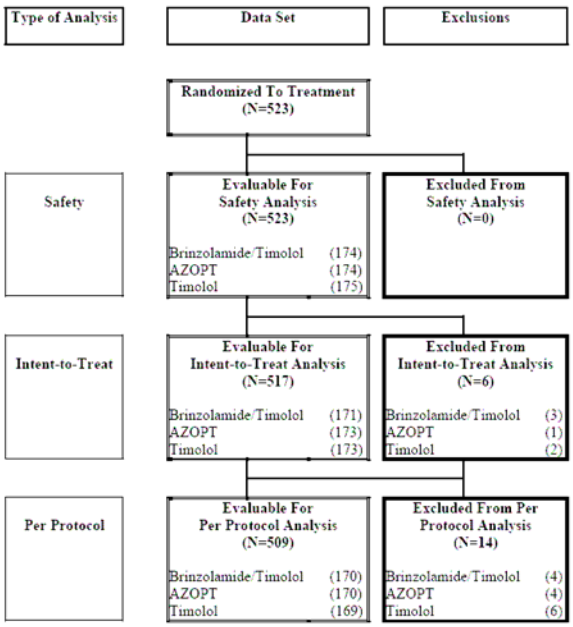


Table 10.1.-2:
Reasons for Study Discontinuation
(Safety Population)

	Brinzolamide/ Timolol (N=174)		AZOPT (N=174)		Timolol (N=175)		Total (N=523)	
	N	%	N	%	N	%	N	%
Total	**13**	**7.5**	**20**	**11.5**	**13**	**7.4**	**46**	**8.8**
Inadequate Control of IOP	1	0.6	14	8.0	3	1.7	18	3.4
Adverse Event	8	4.6	3	1.7	6	3.4	17	3.3
Decision Unrelated to an Adverse Event	1	0.6	0	0.0	0	0.0	1	0.2
Lost to Follow-Up	0	0.0	1	0.6	2	1.1	3	0.6
Non-Compliance	0	0.0	1	0.6	1	0.6	2	0.4
Other	3[a]	1.7	1[b]	0.6	1[c]	0.6	5	1.0

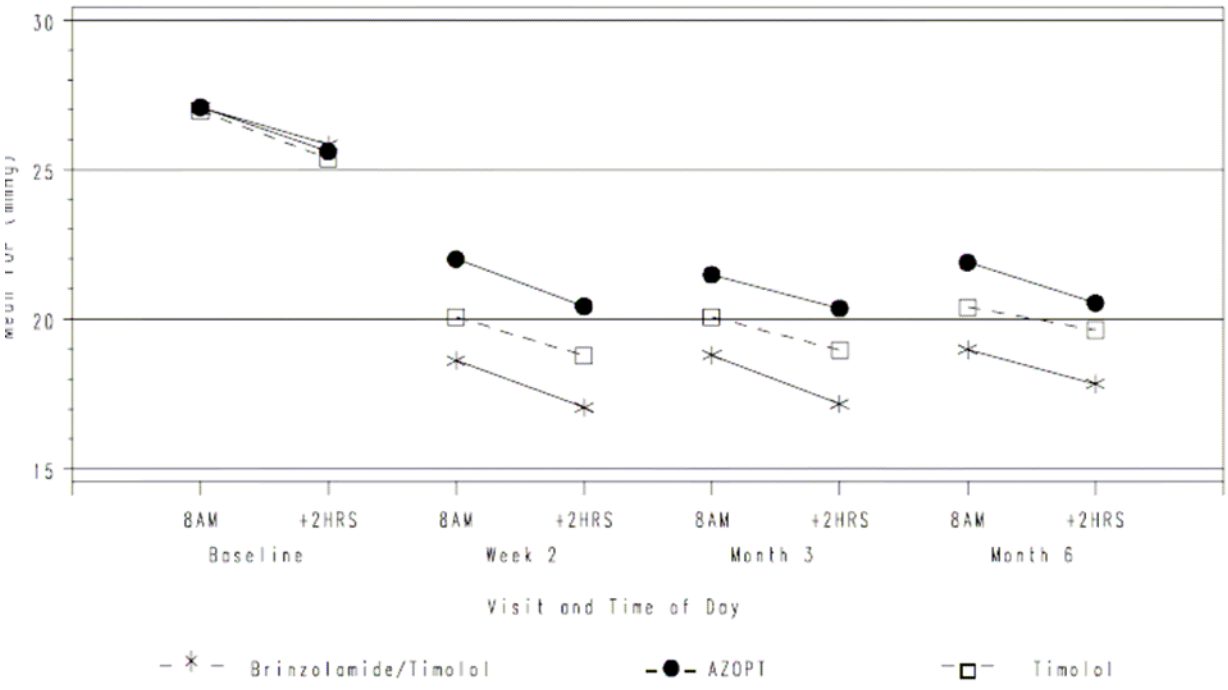
Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension

A higher proportion of patients discontinued study in the group of AZARGA as compared to Azopt and Timolol due to safety reasons (4.6% vs 1.7% and 3.4%, respectively) whilst less patients discontinued due to inadequate control of IOP (0.6% vs 8% and 1.7%, respectively).

The results of this contribution of elements study showed statistically significant mean IOP reductions for all three treatment groups, which ranged from 8.0 to 8.7 mmHg for the AZARGA group, 5.1 to 5.6 mmHg for the Azopt group and 5.7 to 6.9 mmHg for the timolol 5 mg/ml Eye Drops. Superiority of AZARGA over timolol and Azopt was demonstrated for each of the efficacy variables. The magnitude of the effect was consistent with previous similar studies performed with the unfixed combination. Results of the responder analysis confirm the superiority and the clinical relevance of the benefit of the fixed dose combination over its individual components, with a responder rates at 8AM, the most stringent criteria, at 6-month visit of 34.5%, 24.9% and 16.2% for AZARGA, timolol and Azopt, respectively.

Results of the primary endpoint are illustrated in the figure below:

Mean IOP (mmHg) for All Treatments
(Intent-to-Treat Data)



As seen below in the next tables, the difference between the fixed combination and Brinzolamide, respectively Timolol, is statistically significant as concerns the mean IOP.

Comparison of Mean IOP (mmHg)
(Intent-to-Treat Data)
Brinzolamide/Timolol versus AZOPT

	Baseline[a]		Combined		Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS
Brinzolamide/ Timolol										
Mean	27.1	25.8	18.8	17.4	18.6	17.1	18.8	17.2	19.0	17.8
N	171	171	171	171	170	170	171	171	171	171
AZOPT										
Mean	27.1	25.6	21.8	20.4	22.0	20.4	21.5	20.4	21.9	20.5
N	173	173	173	173	172	172	173	173	173	173
Difference	0.0	0.2	-3.0	-3.1	-3.3	-3.3	-2.7	-3.2	-2.9	-2.7
P-value	0.9816	0.4492	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Upper 95% CI	0.6	0.8	-2.2	-2.3	-2.5	-2.5	-1.8	-2.4	-2.1	-1.9
Lower 95% CI	-0.6	-0.4	-3.7	-3.8	-4.2	-4.2	-3.5	-4.0	-3.7	-3.5

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
AZOPT = Brinzolamide 10 mg/ml Eye Drops, Suspension
[a]Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Combined = Results pooled across Week 2, Month 3 and Month 6
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.
P-values and confidence intervals were based on repeated measures analysis of variance.

Comparison of Mean IOP (mmHg)
(Intent-to-Treat Data)
Brinzolamide/Timolol versus Timolol

	Baseline[a]		Combined		Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS
Brinzolamide/ Timolol										
Mean	27.1	25.8	18.8	17.4	18.6	17.1	18.8	17.2	19.0	17.8
N	171	171	171	171	170	170	171	171	171	171
Timolol										
Mean	27.0	25.4	20.2	19.1	20.1	18.8	20.1	19.0	20.4	19.6
N	173	173	173	173	173	173	173	173	173	173
Difference	0.1	0.5	-1.4	-1.8	-1.4	-1.7	-1.3	-1.8	-1.4	-1.8
P-value	0.6784	0.1192	0.0003	<.0001	0.0008	<.0001	0.0031	<.0001	0.0011	<.0001
Upper 95% CI	0.7	1.0	-0.6	-1.0	-0.6	-0.9	-0.4	-1.0	-0.6	-1.0
Lower 95% CI	-0.5	-0.1	-2.1	-2.5	-2.2	-2.6	-2.1	-2.6	-2.2	-2.6

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Combined = Results pooled across Week 2, Month 3 and Month 6
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.
P-values and confidence intervals were based on repeated measures analysis of variance.

The mean change in IOP from baseline is illustrated below:

Mean IOP Change from Baseline (mmHg)
Estimates and 95% Confidence Intervals
(Intent-to-Treat Data)

	Baseline[a]		Combined		Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS
Brinzolamide/ Timolol										
Mean	27.1	25.8	-8.3	-8.5	-8.4	-8.7	-8.3	-8.7	-8.1	-8.0
N	171	171	171	171	170	170	171	171	171	171
P-value	--	--	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Upper 95% CI	27.5	26.2	-7.8	-8.0	-7.9	-8.2	-7.8	-8.1	-7.6	-7.5
Lower 95% CI	26.7	25.4	-8.7	-8.9	-9.0	-9.3	-8.8	-9.2	-8.6	-8.5
AZOPT										
Mean	27.1	25.6	-5.3	-5.2	-5.1	-5.2	-5.6	-5.3	-5.2	-5.1
N	173	173	173	173	172	172	173	173	173	173
P-value	--	--	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Upper 95% CI	27.5	26.0	-4.9	-4.7	-4.6	-4.7	-5.1	-4.7	-4.7	-4.5
Lower 95% CI	26.7	25.2	-5.7	-5.6	-5.6	-5.7	-6.1	-5.8	-5.7	-5.6
Timolol										
Mean	27.0	25.4	-6.8	-6.2	-6.9	-6.6	-6.9	-6.4	-6.6	-5.7
N	173	173	173	173	173	173	173	173	173	173
P-value	--	--	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Upper 95% CI	27.4	25.8	-6.4	-5.8	-6.4	-6.1	-6.4	-5.9	-6.1	-5.2
Lower 95% CI	26.6	25.0	-7.2	-6.7	-7.4	-7.1	-7.4	-6.9	-7.1	-6.3

	Baseline[a]		Combined		Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
AZOPT = Brinzolamide 10 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Combined = Results pooled across Week 2, Month 3 and Month 6.
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.
P-values and confidence intervals were based on repeated measures analysis of variance.
See Section 16.1.9.5 for analysis results.
P-value is associated with hypothesis test of each least squares mean against 0.

With all 3 therapies, a clinically and statistically significant reduction of the IOP was achieved, as seen in the tables above. The fixed combination was superior to the single components in decreasing the IOP at all on therapy visits during the 6 months study period ($p<0.005$). PP results were consistent with ITT results, thus indicating robustness of the findings.

The second endpoint depicted below shows no statistically significant difference, though the numeric values are consistently higher with the fixed combination than with Timolol monotherapy:

Frequency and Percent of Patients Who Maintained Target IOP < 18 mmHg Through All Post-Dosing Time Points (Intent-to-Treat Data) Brinzolamide/Timolol versus Timolol

	Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS
Brinzolamide/ Timolol						
Total	170	170	171	171	171	171
N	64	53	34	32	26	23
%	37.6	31.2	19.9	18.7	15.2	13.5
Timolol						
Total	173	173	173	173	173	173
N	39	34	24	22	19	17
%	22.5	19.7	13.9	12.7	11.0	9.8
p-value*	0.0023	0.0142	0.1366	0.1263	0.2456	0.2945

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution
mmHg = millimeters of mercury
% = Percent
*p-value from chi-square or Fisher's exact test.

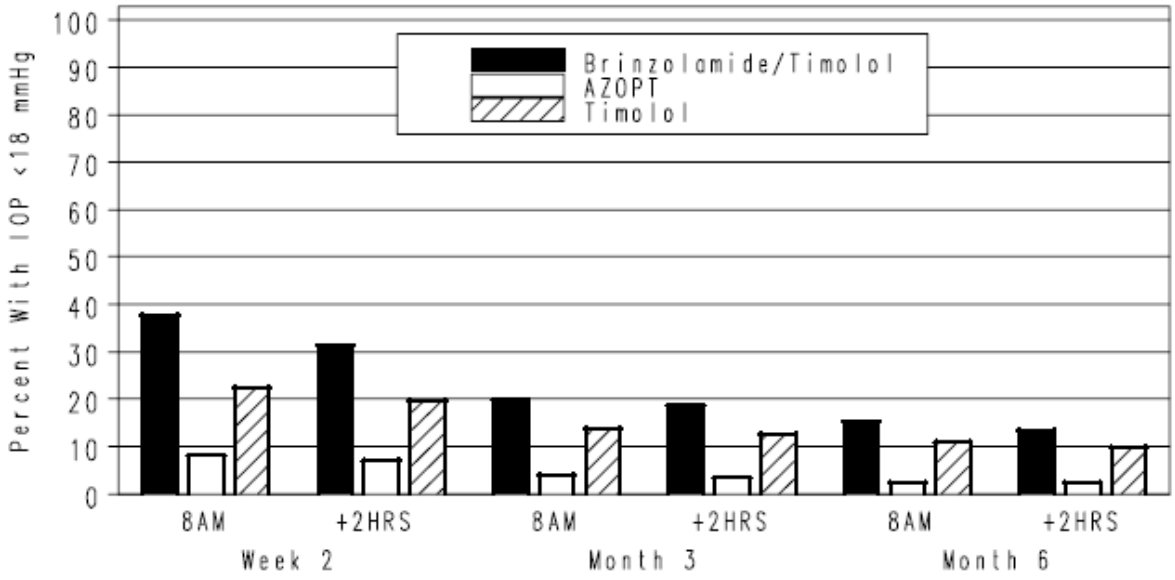
In contrast, the second endpoint depicted below shows a statistically significant difference between the fixed combination and Brinzolamide monotherapy:

Frequency and Percent of Patients Who Maintained Target IOP < 18 mmHg Through All Post-Dosing Time Points (Intent-to-Treat Data) Brinzolamide/Timolol versus AZOPT

	Week 2		Month 3		Month 6	
	8AM	+2 HRS	8AM	+2 HRS	8AM	+2 HRS
Brinzolamide/ Timolol						
Total	170	170	171	171	171	171
N	64	53	34	32	26	23
%	37.6	31.2	19.9	18.7	15.2	13.5
AZOPT						
Total	172	172	173	173	173	173
N	14	12	7	6	4	4
%	8.1	7.0	4.0	3.5	2.3	2.3
p-value*	<.0001	<.0001	<.0001	<.0001	<.0001	0.0001

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
AZOPT = Brinzolamide 10 mg/ml Eye Drops, Suspension
mmHg = millimeters of mercury
% = Percent
*p-value from chi-square or Fisher's exact test.

Frequency and Percent of Patients Who Maintained Target IOP < 18 mmHg Through All Post-Dosing Time Points (Intent-to-Treat Data)



These results demonstrate the superiority and the added benefit of this fixed combination in the reduction of IOP in the target population with respect to the individual components.

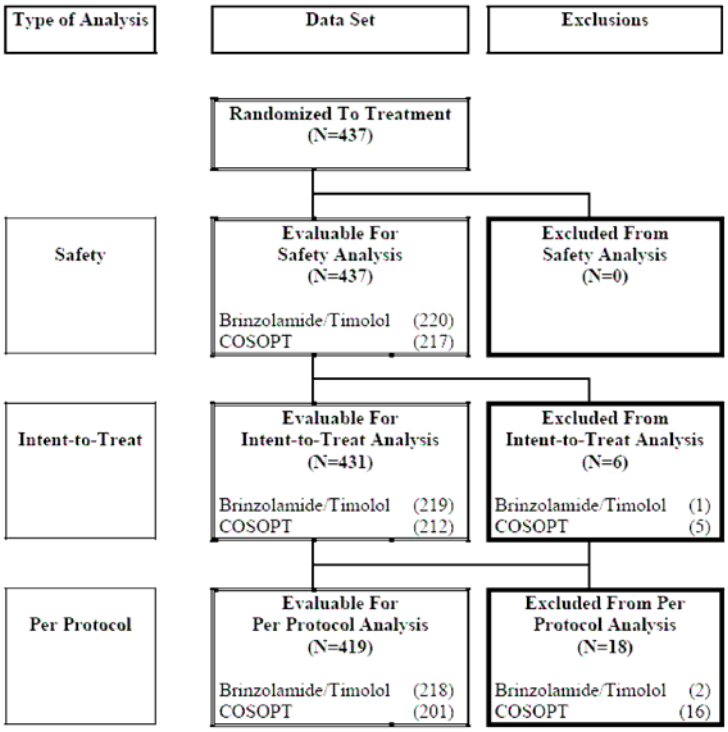
Comparative Study - C-05-10- Pivotal Safety/Efficacy Study

Study C-05-10 was a multinational study conducted at 45 centers in Australia (5), Belgium (2), France (2), Italy (1), Latvia (2), Lithuania (1), Singapore (2), Sweden (1), Taiwan (1), United Kingdom (2), and United States (26). The study was designed to compare the IOP lowering efficacy and safety of AZARGA to that of a marketed fixed combination Cosopt (Dorzolamide 20 mg/ml + timolol 5 mg/ml

Eye Drops, Solution), in patients with open-angle glaucoma or ocular hypertension who were on treatment for IOP-lowering and who could benefit from a combination therapy in the investigator´s view. Both medications were dosed twice daily, at 8 AM and 8 PM. The study was a multicenter, double-masked, parallel group trial with a similar design to Study C-05-24.
The primary objective of this study was to compare the safety and IOP-lowering efficacy of Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension to COSOPT in patients with open-angle glaucoma or ocular hypertension.

The primary efficacy parameter was mean IOP at 8:00 AM, 10:00 AM (+2 hours post dose) and 4:00 PM (+8 hours post dose). Primary efficacy analysis was based on the Month 6 assessments at 8:00 AM, 10:00 AM and 4:00 PM.
The patients continued to be followed for up to an additional 6 months to enable the collection of additional safety information.

Table 10.1.-3:
Disposition of Randomized, Efficacy-Evaluated, and Safety-Evaluated Patients



Of the 437 randomized patients, 393 completed the study and 44 (16 on Brinzolamide 10 mg/ml + timolol 5 mg/ml Eye Drops, Suspension and 28 on Cosopt) discontinued prior to completion. Six patients were excluded from the overall intent-to-treat (ITT) analysis due to an absence of any on-therapy efficacy data. Eighteen patients were excluded from the overall per protocol analysis due to the following reasons: an absence of any on-therapy efficacy data (6 patients), use of an excluded concomitant medication (1 patient), non-qualifying IOP at study entry (4 patients), patient not on IOP-lowering medication at study entry (3 patients), patient non-compliance (1 patient), inadequate washout from previous IOP-lowering medication (2 patients) and failure to meet inclusion criterion (1 patient).

Table 10.1.-2:
Reasons for Study Discontinuation
(Safety Population)

	Brinzolamide/ Timolol (N=220)		COSOPT (N=217)		Total (N=437)	
	N	%	N	%	N	%
Total	**16**	**7.3**	**28**	**12.9**	**44**	**10.1**
Inadequate Control of IOP	5	2.3	5	2.3	10	2.3
Adverse Event	8	3.6	13	6.0	21	4.8
Decision Unrelated to an Adverse Event	1	0.5	2	0.9	3	0.7
Lost to Follow-Up	2	0.9	2	0.9	4	0.9
Non-Compliance	0	0.0	1	0.5	1	0.2
Other	0	0.0	5[a]	2.3	5	1.1

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension

Mean IOP at 8AM baseline were 27.3 mmHg (26.9-27.7 mmHg, 95%CI) in both treatment groups.

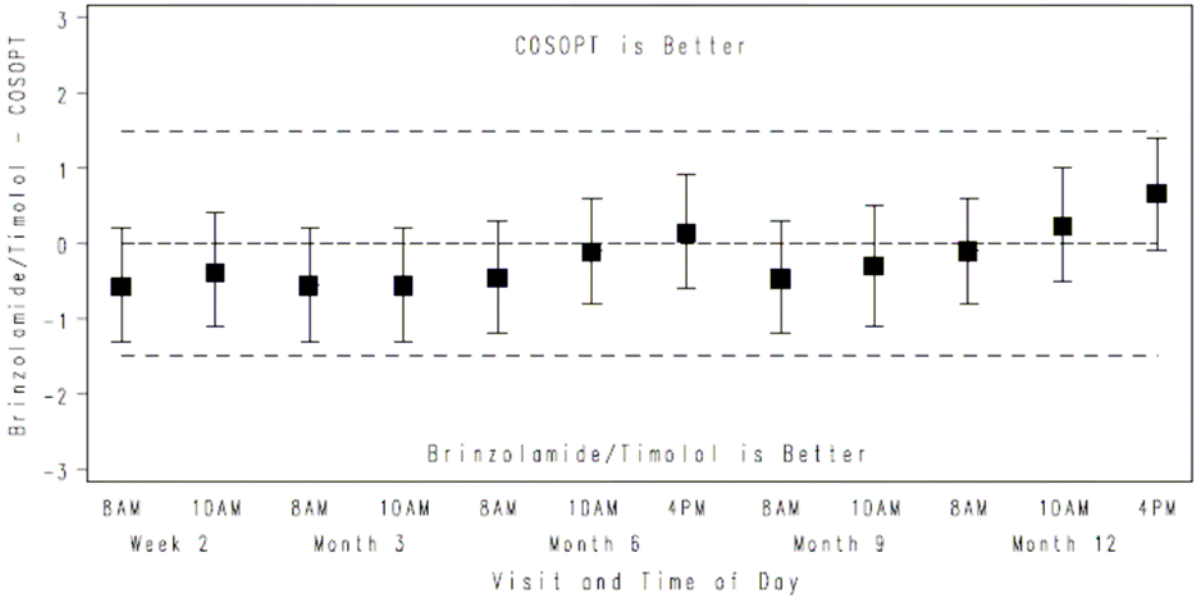
Results of the primary endpoint are shown below:

Comparison of Mean IOP (mmHg)
(Per Protocol Data)
Brinzolamide/Timolol versus COSOPT

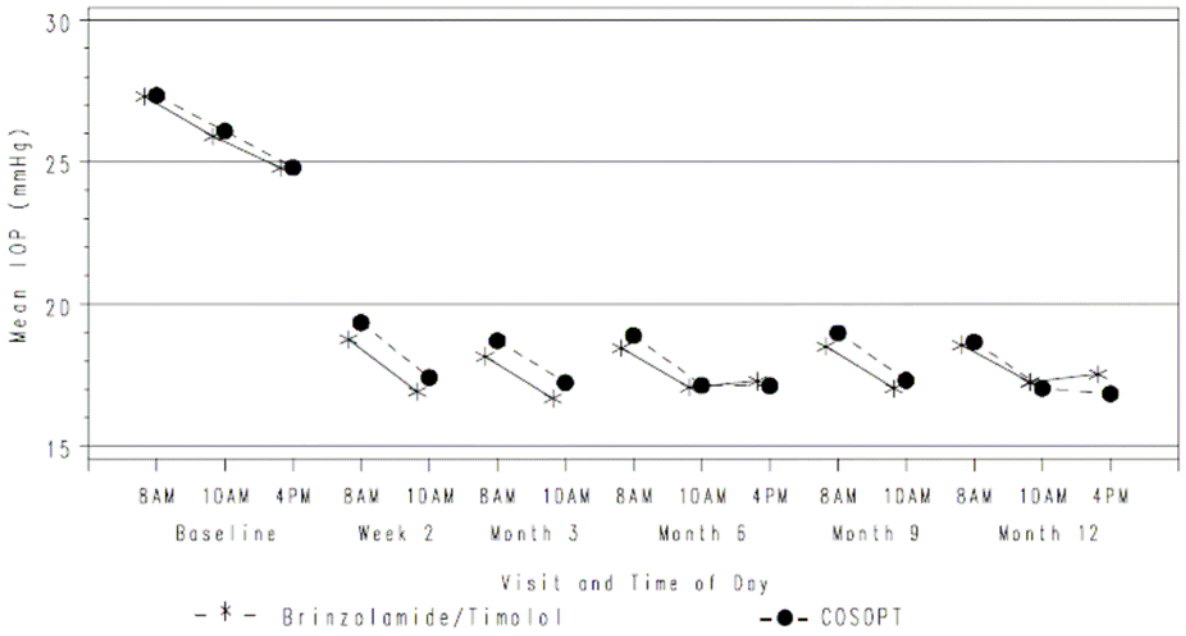
		Brinzolamide/Timolol		COSOPT					
		Mean	N	Mean	N	Difference	P-value	Upper 95% CI	Lower 95% CI
Baseline[a]	**8AM**	27.3	218	27.3	201	-0.0	0.9099	0.6	-0.7
	10AM	25.9	218	26.1	201	-0.2	0.5593	0.4	-0.8
	4PM	24.8	218	24.8	201	-0.0	0.9708	0.6	-0.6
Week 2	**8AM**	18.8	216	19.3	198	-0.6	0.1267	0.2	-1.3
	10AM	17.0	195	17.4	185	-0.4	0.3020	0.4	-1.1
Month 3	**8AM**	18.2	208	18.7	187	-0.6	0.1230	0.2	-1.3
	10AM	16.7	207	17.2	186	-0.6	0.1252	0.2	-1.3
Month 6	**8AM**	18.5	205	18.9	181	-0.5	0.2235	0.3	-1.2
	10AM	17.1	204	17.2	181	-0.1	0.7512	0.6	-0.8
	4PM	17.3	200	17.2	180	0.1	0.7014	0.9	-0.6
Month 9	**8AM**	18.5	198	19.0	173	-0.5	0.2297	0.3	-1.2
	10AM	17.0	198	17.3	173	-0.3	0.4349	0.5	-1.1
Month 12	**8AM**	18.6	191	18.7	169	-0.1	0.7843	0.6	-0.8
	10AM	17.2	192	17.0	168	0.2	0.5491	1.0	-0.5
	4PM	17.5	192	16.9	168	0.7	0.0782	1.4	-0.1

Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
COSOPT = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.
P-values and confidence intervals were based on repeated measures analysis of variance.

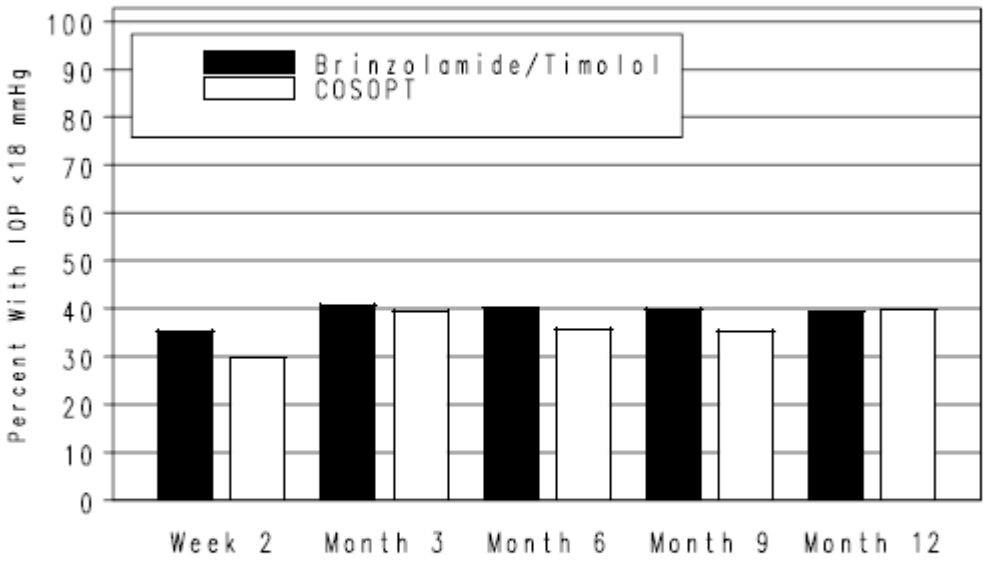
IOP (mmHg) Least Squares Means Differences Between Brinzolamide/Timolol and COSOPT and 95% Confidence Intervals (Per Protocol Data)



Mean IOP (mmHg) for Brinzolamide/Timolol and COSOPT (Per Protocol Data)



Percentage of Patients Who Achieved Target IOP <18 mmHg at 8AM Visit
(Per Protocol Data)



Brinzolamide/Timolol = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension

COSOPT = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution

AZARGA produced IOP-lowering efficacy that was non-inferior to Cosopt. The per protocol analyses demonstrate that the upper 95% confidence limits were within +1.5 mmHg, the limit of clinical relevance used to establish non-inferiority in this study, at all study visits and times. The largest value observed for the upper 95% confidence limit was +1.4 mmHg in the per protocol analysis, and +1.3 mmHg in the intent-to-treat analysis.
Difference in mean IOP favoured AZARGA over Cosopt at 9 of 12 study visits and times and ranged from -0.6 mmHg to +0.7 mmHg in the per protocol analysis. Following dosing with AZARGA, mean IOP ranged from 17.0 mmHg to 18.6 mmHg. Following dosing with Cosopt, mean IOP ranged from 17.2 to 19.3 mmHg. Mean IOP reductions from baseline for AZARGA were clinically relevant and statistically significant at all measurement times. The IOP reduction ranged from -7.2 to -9.2 mmHg for AZARGA and from -7.7 to -8.8 mmHg for Cosopt in the per protocol analysis.
The descriptive results for mean percent IOP change show that the mean reductions for AZARGA equate to percent reductions ranging from 28.4% to 34.9% relative to baseline.

The clinical relevance of the IOP reductions was demonstrated by the percent of patients in each treatment group who responded to treatment. Patients were considered to have a clinically relevant response to treatment at a visit if their IOP decreased to less than 18 mmHg at least 1 time point (when evaluated at each visit, up to 61% of patients in the AZARGA group and up to 59% of patient in the Cosopt group had IOP of less than 18 mmHg). At 6-month 8AM, the rate of responders were 40% and 35.9% in AZARGA and Cosopt, respectively. These percentages were maintained at 9-month 8AM visit and the difference was even lower at 12-month (39% and 40%, respectively).
Results were consistent between the per protocol and intent-to-treat analyses.

Descriptive Mean Results for IOP (mmHg), IOP Change from Baseline (mmHg), and Percent IOP Change from Baseline (C-05-10, Per Protocol Data)

	Week 2		Month 3		Month 6			Month 9		Month 12		
Treatment	8AM	10AM	8AM	10AM	8AM	10AM	4PM	8AM	10AM	8AM	10AM	4PM
AZARGA												
Mean IOP	18.8	16.9	18.2	16.7	18.5	17.1	17.3	18.5	17.0	18.6	17.3	17.5
Mean IOP Change	-8.5	-8.9	-9.1	-9.1	-8.8	-8.8	-7.5	-8.7	-8.8	-8.7	-8.6	-7.2
Mean % IOP Change	-31.1	-34.1	-33.3	-34.9	-32.1	-33.5	-29.5	-31.9	-33.3	-31.7	-32.7	-28.4
N	216	195	208	207	205	204	200	198	198	191	192	192
COSOPT												
Mean IOP	19.4	17.4	18.7	17.2	18.9	17.1	17.1	19.0	17.3	18.7	17.0	16.9
Mean IOP Change	-8.0	-8.7	-8.7	-8.8	-8.3	-8.7	-7.4	-8.2	-8.6	-8.5	-8.9	-7.7
Mean % IOP Change	-29.2	-33.0	-31.6	-33.5	-30.4	-33.4	-29.7	-30.2	-33.1	-31.2	-33.9	-30.7
N	198	185	187	186	181	181	180	173	173	169	168	168

AZARGA = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
COSOPT = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution
Estimates based on descriptive statistics.

Pre-Study IOP-Lowering Medications in AZARGA Pivotal Studies (C-05-24 and C-05-10)

Number of Medications	All Studies (N=943)		C-05-24 (N=511[b])		C-05-10 (N=432[a])	
	N	%	N	%	N	%
0	127	13.5	125	24.5	2	0.5
1	614	65.1	304	59.5	310	71.8
2	162	17.2	60	11.7	102	23.6
3 or 4	40	4.2	22	4.3	18	4.2

[a] Pre-study medications for 5 patients did not satisfy criteria for inclusion in C-05-10 analysis
[b] Pre-study medications for 12 patients did not satisfy criteria for inclusion in C-05-24 analysis

In Study C-05-10 the vast majority (71.8%) of patients was on monotherapy and according to the investigator judgment could benefit from a combination therapy. Furthermore at study recruitment, 13.5 % of patients overall did not receive anti-glaucoma medication. It remains to be proven that these patients would need a combination therapy. A justification for that some (or any) of the patients would not be sufficiently controlled on a β-blocker – or on brinzolamide – in monotherapy, was missing.
According to its SPC, the use of Cosopt should be restricted to patients with insufficient IOP response to beta-blockers and thus, one might consider that the efficacy of Cosopt in such a broad study population is unknown and so the comparison is unbalanced. Even though this does not necessarily mean that patients were insufficiently responsive to previous treatment, this population represented the main target population and as such, it was considered valid. Patients on previous treatment with 2 (N=102, 23.6%) or even 3 or 4 IOP-lowering drugs (N=18, 4.2%) were also included. These patients might also represent a subset of the target population. As a consequence, a broad second or even third line indication was initially sought.
The CHMP raised a major objection on this point, and requested the Applicant to provide data on the type of previous IOP decreasing medication and efficacy results for the sub-group of patients for whom there is general agreement on being considered insufficient responders (i.e. those with IOP-values ≥22 mm Hg) while on treatment before the wash-out phase. The answer of the Applicant is discussed below in the section "Analysis performed across trials".

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

In the initial application, neither pooled analyses nor meta-analysis have been presented.

The answer of the Applicant to the Day 180 list of Outstanding issues showed that 113/417 patients (27.1 %), with IOP ≥ 22 mmHg did not receive any anti-glaucoma mediation at inclusion. This was driven by results from study C-05-24 in which the figure was 112/260 (43.1 %). This is a large number considering the usual approach for prescribing a combination drug.

Table 3-2:
Number of Pre-Study IOP-Lowering Medications in AZARGA Pivotal Studies where Screening IOP ≥ 22 mmHg
(C-05-24, C-05-10 and Pooled Data, Intent-to-Treat Data)

Number of Medications	Pooled (N=417)		C-05-24 (N=260)		C-05-10 (N=157)	
	N	%	N	%	N	%
0	113	27.1	112	43.1	1	0.6
1	241	57.8	118	45.4	123	78.3
2	48	11.5	19	7.3	29	18.5
3 or 4	15	3.6	11	4.2	4	2.5

Tables 3-3 and 3-4 provide the mean IOP and IOP change from baseline results for patients with Screening IOP ≥ 22 mmHg while on pre-study medication(s) for studies C-05-24 and C-05-10, respectively. The results of these analyses demonstrate that the IOP-lowering efficacy of AZARGA in the sub-population of patients with IOP ≥ 22 mmHg while on pre-study medication(s) is consistent with that of the total population. This is confirmed by the results of the comparisons between AZARGA and Azopt (Table 3-6), and between AZARGA and timolol (Table 3-7) from the contribution of elements study C-05-24, which demonstrate superiority of AZARGA at all time-points. Similarly, the results for study C-05-10 presented in Table 3-8 confirm that AZARGA is non-inferior to Cosopt in patients with Screening IOP ≥ 22 mmHg while on 1 or more IOP lowering medication(s).

Table 3-3
Mean IOP (mmHg) in Patients with Screening IOP ≥ 22 mmHg and 1 or More Pre-Study IOP-Lowering Medication
(C-05-24, Intent-to-Treat Data)

		Baseline		Week 2		Month 3		Month 6	
		8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM
AZARGA	Mean IOP	27.9	27.2	19.5	18.2	19.7	18.3	20.1	19.2
	Mean IOP Change	--	--	-8.4	-8.9	-8.2	-8.9	-7.8	-8.0
	Mean % IOP Change	--	--	-29.7	-32.2	-28.8	-31.8	-27.4	-28.7
	N	53	53	52	52	53	53	53	53
AZOPT	Mean IOP	28.5	27.5	24.1	22.6	24.0	23.3	24.6	23.4
	Mean IOP Change	--	--	-4.4	-4.8	-4.5	-4.1	-4.0	-4.1
	Mean % IOP Change	--	--	-15.6	-17.7	-15.9	-15.3	-14.1	-15.6
	N	48	48	48	48	48	48	48	48
Timolol	Mean IOP	28.6	27.3	22.5	21.5	22.8	21.4	23.4	22.5
	Mean IOP Change	--	--	-6.1	-5.8	-5.8	-5.9	-5.2	-4.8
	Mean % IOP Change	--	--	-21.5	-21.4	-20.6	-21.6	-18.2	-18.0
	N	47	47	47	47	47	47	47	47

Table 3-4:
Mean IOP (mmHg) in Patients Treated with Screening IOP ≥ 22 mmHg and 1 or More Pre-Study IOP-Lowering Medication (C-05-10, Intent-to-Treat Data)

		Baseline		Week 2		Month 3		Month 6		Month 9		Month 12	
		8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM
AZARGA	Mean IOP	28.2	27.3	20.5	18.9	19.3	18.0	19.8	18.4	19.7	17.8	19.6	18.1
	Mean IOP Change	--	--	-7.7	-8.5	-8.9	-9.3	-8.4	-9.0	-8.5	-9.5	-8.5	-9.2
	Mean % IOP Change	--	--	-27.0	-30.2	-31.3	-33.2	-29.3	-32.0	-29.7	-34.2	-29.9	-32.9
	N	71	71	71	71	71	71	71	71	71	71	71	71
Cosopt	Mean IOP	28.0	27.0	20.5	19.1	19.9	18.6	20.4	19.0	20.6	19.2	19.9	18.8
	Mean IOP Change	--	--	-7.4	-7.9	-8.1	-8.4	-7.5	-8.1	-7.3	-7.8	-8.0	-8.2
	Mean % IOP Change	--	--	-26.4	-29.1	-28.8	-30.8	-27.0	-29.7	-26.1	-28.6	-28.6	-30.0
	N	85	85	85	85	85	85	85	85	85	85	85	85

Table 3-5
Mean IOP (mmHg) in Patients Treated with AZARGA and Screening IOP ≥ 22 mmHg and 1 or More Pre-Study IOP-Lowering Medications (Pooled C-05-24 and C-05-10, Intent-to-Treat Data)

		Baseline		Week 2		Month 3		Month 6		Month 9		Month 12	
		8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM	8 AM	10 AM
No. of Medications:													
1 or More Medications	Mean IOP	28.0	27.3	20.0	18.6	19.5	18.1	19.9	18.7	19.7	17.8	19.6	18.1
	Mean IOP Change	--	--	-8.0	-8.7	-8.6	-9.1	-8.1	-8.6	-8.5	-9.5	-8.5	-9.2
	Mean % IOP Change	--	--	-28.1	-31.1	-30.2	-32.6	-28.5	-30.6	-29.7	-34.2	-29.9	-32.9
	N	124	124	123	123	124	124	124	124	71	71	71	71

Table 3-6:
Comparison of Mean IOP (mmHg) for Patients with a Screening IOP ≥ 22 mmHg and 1 or More Pre-Study IOP-Lowering Medications (C-05-24, Intent-to-Treat Data)

AZARGA versus AZOPT

		AZARGA		AZOPT					
		Mean	N	Mean	N	Difference	P-value	Upper 95% CI	Lower 95% CI
Baseline[a]	8AM	27.9	53	28.5	48	-0.6	0.2923	0.6	-1.8
	10AM	27.2	53	27.5	48	-0.3	0.6514	0.9	-1.5
Combined	8AM	19.8	53	24.2	48	-4.5	<.0001	-3.0	-5.9
	10AM	18.6	53	23.1	48	-4.6	<.0001	-3.1	-6.0
Week 2	8AM	19.5	52	24.1	48	-4.6	<.0001	-2.9	-6.2
	10AM	18.2	52	22.6	48	-4.4	<.0001	-2.8	-6.1
Month 3	8AM	19.7	53	24.0	48	-4.3	<.0001	-2.7	-6.0
	10AM	18.3	53	23.3	48	-5.0	<.0001	-3.4	-6.7
Month 6	8AM	20.1	53	24.6	48	-4.4	<.0001	-2.8	-6.1
	10AM	19.2	53	23.4	48	-4.2	<.0001	-2.6	-5.9

AZARGA = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
AZOPT = Brinzolamide 10 mg/ml Eye Drops, Suspension
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Combined = Results pooled across Week 2, Month 3 and Month 6
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.

Table 3-7:
Comparison of Mean IOP (mmHg) for Patients with a Screening IOP ≥ 22 mmHg and 1 or More Pre-Study IOP-Lowering Medications (C-05-24, Intent-to-Treat Data)

AZARGA versus Timolol

		AZARGA		Timolol					
		Mean	N	Mean	N	Difference	P-value	Upper 95% CI	Lower 95% CI
Baseline[a]	8AM	27.9	53	28.6	47	-0.7	0.2419	0.5	-1.9
	10AM	27.2	53	27.3	47	-0.1	0.8812	1.1	-1.3
Combined	8AM	19.8	53	22.9	47	-3.1	<.0001	-1.6	-4.6
	10AM	18.6	53	21.8	47	-3.2	<.0001	-1.7	-4.7
Week 2	8AM	19.5	52	22.5	47	-3.0	0.0005	-1.3	-4.6
	10AM	18.2	52	21.5	47	-3.3	0.0001	-1.6	-4.9
Month 3	8AM	19.7	53	22.8	47	-3.1	0.0003	-1.4	-4.7
	10AM	18.3	53	21.4	47	-3.1	0.0003	-1.4	-4.7
Month 6	8AM	20.1	53	23.4	47	-3.3	0.0001	-1.6	-5.0
	10AM	19.2	53	22.5	47	-3.3	0.0001	-1.6	-5.0

AZARGA = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Combined = Results pooled across Week 2, Month 3 and Month 6
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.

Table 3-8
Comparison of Mean IOP (mmHg) with a Screening IOP ≥ 22 mmHg and 1 or More Pre-Study IOP-Lowering Medications (C-05-10, Intent-to-Treat Data)

AZARGA versus COSOPT

		AZARGA		COSOPT					
		Mean	N	Mean	N	Difference	P-value	Upper 95% CI	Lower 95% CI
Baseline[a]	8AM	28.2	71	28.0	85	0.2	0.7075	1.2	-0.8
	10AM	27.3	71	27.0	85	0.3	0.5692	1.3	-0.7
Combined	8AM	19.8	71	20.3	85	-0.5	0.3320	0.5	-1.5
	10AM	18.2	71	18.9	85	-0.7	0.1765	0.3	-1.7
Week 2	8AM	20.5	71	20.5	85	-0.1	0.9186	1.2	-1.3
	10AM	18.9	71	19.1	85	-0.2	0.6965	1.0	-1.5
Month 3	8AM	19.3	71	19.9	85	-0.6	0.3312	0.6	-1.9
	10AM	18.0	71	18.6	85	-0.6	0.3354	0.6	-1.9
Month 6	8AM	19.8	71	20.4	85	-0.6	0.3157	0.6	-1.9
	10AM	18.4	71	19.0	85	-0.6	0.3537	0.7	-1.8
Month 9	8AM	19.7	71	20.6	85	-1.0	0.1305	0.3	-2.2
	10AM	17.8	71	19.2	85	-1.4	0.0234	-0.2	-2.7
Month 12	8AM	19.6	71	19.9	85	-0.3	0.6537	1.0	-1.5
	10AM	18.1	71	18.8	85	-0.7	0.2806	0.6	-1.9

AZARGA = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
COSOPT = Dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution
[a] Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.
CI = Confidence interval
Combined = Results pooled across Week 2, Month 3, Month 6, Month 9 and Month 12
Estimates based on least squares means using repeated measures analysis of variance. Baseline estimates obtained from separate model.

After evaluation of the Applicant's answer, it can be concluded that the efficacy of AZARGA eye drops in the subpopulation with an IOP ≥ 22 mmHg at inclusion and treated with at least one anti-glaucoma medication is justified. The IOP decreasing effect of the eye drops in this population was consistent to what was observed for the full study population.

Clinical studies in special populations

Paediatric patients

No study has been conducted with AZARGA in paediatric patients. No paediatric investigation plan has been submitted.
Paediatric data are available for AZOPT and timolol:
In 1 clinical study (C-00-17), AZOPT was administered to 32 paediatric patients (1 week to 6 years of age). In this study, AZOPT effectively maintained or reduced IOP in paediatric patients with glaucoma or ocular hypertension. IOP-lowering efficacy was similar to that in adult patients and could provide benefit to those paediatric patients requiring IOP-lowering medication. These data have been assessed by the CHMP and a Type II variation (No. II/0025) including the relevant information in the SPC / PIL was approved in June 2007.
Furthermore, the Applicant has collected data on 71 paediatric patients (1 week to 6 years of age) exposed to timolol Ophthalmic Gel Forming Solution, 2.5 or 5 mg/ml (Clinical Study C-01-01). In this study, timolol Ophthalmic Gel Forming Solution, 2.5 and 5 mg/ml effectively reduced IOP in paediatric patients.
Considering the lack of data, the proposal not to recommend the use of AZARGA in children below 18 years due to a lack of data on safety and efficacy is considered acceptable.

Other special populations
No specific studies were conducted.

Supportive studies

Supportive evidence comes from co-administration studies. These studies had previously been submitted and assessed as part of the MAA of Azopt and are not discussed here.

Discussion on clinical efficacy

The existence of a fixed dosage combination of brinzolamide and timolol is considered justified according to the Guideline on fixed combination medicinal products, and based on valid therapeutic principles. A simplification of therapy which improves patient compliance, a known factor of possible improvement in IOP control, supports the advantages of this fixed combination.

The benefit of the concomitant administration of brinzolamide plus timolol was demonstrated at the time of gaining the marketing authorisation for Azopt. The current clinical development programme is aimed to support the benefit of the fixed dose combination of brinzolamide/timolol eye drops, solution with a well designed programme that documents the contribution of elements within the combination as well as comparative benefit over a reference treatment. AZARGA produces greater mean IOP reductions than those produced by either Brinzolamide or timolol alone. Also, the non-inferiority of the fixed combination over the currently marketed fixed dose combination of another carbonic anhydrase inhibitor and timolol (Cosopt) has been shown. Therefore, the efficacy requirements for a fixed dose combination therapy have been demonstrated.

The CHMP concluded that although the data confirming the efficacy of AZARGA in the target population of open angle glaucoma or ocular hypertension is based on a limited number of patients, namely an ITT population of 124 patients treated with AZARGA, the demonstrated effect was convincing and robust. Although the approach of the study programme to some extent is failed, resulting in a limited number of appropriate/target patients, the provided analyses demonstrate/contribute evidence of a clinical efficacy in these patients.

The Applicant had justified that the efficacy in the selected, clinically relevant population the efficacy is consistent with results for the full population. Although the dossier is not ideal, the Applicant's response was acceptable, and a MA could be granted provided that the Applicant can accept the CHMP proposal for a revised wording of the indication, as it was not the intention of the clinical trials carried out with AZARGA to show a benefit in patients not tolerant to their current IOP medication. Furthermore, patients being treated with monotherapy who are not tolerant to their medication may switch to a different active substance in monotherapy as well before starting a combination product.

Therefore, the initially proposed therapeutic indication:
Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction or is not well tolerated (see section 5.1)

Was reworded to:
"Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction (see section 5.1)"

This broad indication allows for a second line indication following monotherapy treatment with either timolol, prostaglandin analogues, alpha agonist, etc, but would allow for a third line indication as well.

In summary, across all analyses presented on the total population, as part of the initial application, and on multiple patient subgroups provided in response to the Day 120 List of Questions and the response to the Day 180 List of Outstanding Issues, the results have demonstrated that the efficacy of AZARGA is superior to that of the individual components, and non-inferior to that of the active comparator Cosopt.

Clinical safety

Patient exposure

Duration of Exposure to AZARGA by Clinical Study

Study	Total Number of Patients	Number of Patients on AZARGA	Total Duration of Dosing AZARGA	
			≥ 180 days	≥ 350 days (1 year[a])
C-97-22	66	33	0	0
C-05-27	87	26	0	0
C-05-10	437	220	214	200
C-05-24	523	174	140	0
C-05-49	95[c]	48	0	0
Total	**1203**[b]	**501**	**354**	**200**

[a] 1 year is defined as ≥ 351 days due to the Month 12 Visit window [± 14 days] specified in the protocol

[b] This total only includes topical ocular dosing. Patients in protocol C-05-27 received either brinzolamide 1 mg capsules or placebo capsules before they were randomised to the topical ocular phase. Five patients in C-05-27 were not randomised into the topical ocular phase of the study and are therefore not reflected in the total number of patients

[c] 96 patients were randomised, 1 patient never dosed and is excluded from this table

AZARGA = brinzolamide 10 mg/ml + timolol 5 mg/ml Eye Drops, Suspension

The size and distribution of the safety database is satisfactory for long term use of these two well established components: In the pivotal trials, the age of range 22 to 90 years, with 57.8% vs. 42.2 % female and male patients, respectively is unremarkable. A total of 78.2 % of the patients were Caucasian, 16.4 % were Black.

Adverse events
An adequate battery appropriate for the evaluation of the test drug in patients with glaucoma/ocular hypertension has been applied.

A summary of the frequency, incidence, and nature of adverse events in the phase III studies is shown in the tables below:

Frequency and Incidence of Patients With Adverse Drug Reactions

	Total N	Patients with Adverse Drug Reactions N	%
Total	**1203**	**205**	**17.1%**
AZARGA	501	82	16.2
Cosopt	264	71	26.9
Azopt	202	28	13.9
Timolol	236	24	10.2

Adverse Drug Reaction = treatment-related adverse event
AZARGA = brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
Cosopt = dorzolamide 20 mg/ml + Timolol 5 mg/ml Eye Drops, Solution
Azopt = brinzolamide 10 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution

The percentage of adverse events with AZARGA, Cosopt, brinzolamide and timolol were 16.2 %, 26.9 %, 13.9 % and 10.2 %, respectively, indicating a numerically larger frequency in the dorzolamide /timolol fixed combination than in the brinzolamide/timolol combination.

All Adverse Drug Reactions - All Studies

Coded Adverse Reactions	Brinzolamide /Timolol N = 501 N	%	Cosopt N = 264 N	%	Azopt N = 202 N	%	Timolol N = 236 N	%
Immune system disorders								
Hypersensitivity			2	0.8				
Psychiatric disorders								
Insomnia	1	0.2						
Nervous system disorders								
Dysgeusia	12	2.4	6	2.3	10	5.0	1	0.4
Headache			3	1.1	1	0.5		
Sinus Headache							1	0.4
Eye disorders								
Vision Blurred	31	6.2	2	0.8	6	3.0	3	1.3
Eye Irritation	19	3.8	31	11.7	5	2.5	7	3.0
Eye Pain	14	2.8	25	9.5	1	0.5	3	1.3
Foreign Body Sensation In Eyes	5	1.0	1	0.4	1	0.5	1	0.4
Punctate Keratitis	3	0.6			1	0.5	3	1.3
Ocular Hyperaemia	3	0.6	4	1.5	1	0.5		
Photophobia	1	0.2	1	0.4	2	1.0	2	0.8
Conjunctival Hyperaemia	3	0.6			2	1.0	1	0.4
Lacrimation Increased	1	0.2	3	1.1			2	0.8
Dry Eye	2	0.4	1	0.4	1	0.5	1	0.4
Eye Pruritus	3	0.6	1	0.4	1	0.5		
Eye Discharge	2	0.4			2	1.0		
Abnormal Sensation In Eye	1	0.2					1	0.4
Blepharitis	1	0.2	1	0.4				

Blepharitis	1	0.2	1	0.4				
Allergic Eyelid Margin Crusting	1	0.2	1	0.4				
Anterior Chamber Flare	1	0.2						
Asthenopia	1	0.2						
Conjunctivitis Allergic	1	0.2						
Corneal Disorder	1	0.2						
Corneal Erosion	1	0.2						
Erythema Of Eyelid	1	0.2						
Eyelids Pruritus	1	0.2						
Scleral Hyperaemia	1	0.2						
Conjunctival Follicles			1	0.4				
Eyelid Oedema					1	0.5	1	0.4
Conjunctival Oedema							1	0.4
Visual Acuity Reduced							1	0.4
Cardiac disorders								
Bradycardia			1	0.4			2	0.8
Respiratory, thoracic and mediastinal disorders								
Pharyngolaryngeal Pain	1	0.2			1	0.5		
Chronic Obstructive Pulmonary Disease	1	0.2						
Cough	1	0.2						
Rhinorrhoea	1	0.2						
Orthopnoea			1	0.4				
Sinus Congestion					1	0.5		
Dyspnoea							1	0.4
Wheezing							1	0.4
Gastrointestinal disorders								
Nausea					2	1.0		
Vomiting					1	0.5		
Skin and subcutaneous tissue disorders								
Hair Disorder	1	0.2						
Lichen Planus	1	0.2						
Periorbital Oedema					1	0.5		
Investigations								
Blood Pressure Decreased	2	0.4	1	0.4				
Intraocular Pressure Decreased	3	0.6						
Heart Rate Decreased			2	0.8			1	0.4
Corneal Staining			1	0.4				

Coded adverse reactions = MedDRA Preferred Terms (version 10.0) presented by System Organ Class
Brinzolamide/Timolol (AZARGA) = Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops, Suspension
Cosopt = dorzolamide 20 mg/ml + Timolol % mg/ml Eye Drops, Solution
Azopt = Brinzolamide 10 mg/ml Eye Drops, Suspension
Timolol = Timolol 5 mg/ml Eye Drops, Solution

The most commonly recorded ocular adverse event for AZARGA was blurred vision (6.2 %), eye irritation (3.8 %), eye pain (2.8 %), and foreign body sensation (1.0 %).

Likewise, the cases of adverse events classified as treatment related are low and do not raise specific concerns.

The topical ocular adverse events do not represent any worrying aspects, either quantitatively or qualitatively. However, the Applicant was asked to provide a review of the increased cup/disc ratio

and visual field defect observed in the AZARGA treated population and explore the impact of the observed larger occurrence in the AZARGA-treated patients. Although the absolute figures are low, a preponderance of these disturbing changes is not excluded in the presented material.
In its answer, the Applicant stated that there are no pharmacological reasons to expect differences between AZARGA and Cosopt. This was endorsed. The lack of statistical differences does not provide evidence for the absence of clinical differences potentially appearing.

Overall, considering the mainly elderly population, the pattern is not unexpected.

Serious adverse events and deaths

Two deaths were reported, one renal cell carcinoma and one unexpected death. The cause of death was identified as a left intracerebral haemorrhage centred on the basal ganglia. There were no autopsy findings to indicate that the intracerebral haemorrhage was due to anything other than natural causes. The Investigator classified the death as not related to the study drug.

No treatment related deaths were reported.

Two serious adverse events recorded as treatment related were reported. One patient in the AZARGA-group developed a decompensation of a previously undiagnosed chronic obstructive pulmonary disease. The second patient had a systemic allergic reaction to study medication, which was Cosopt.

Overall, the frequency and nature of the reports of serious events were considered as not concerning. No specific pattern is revealed, and considering the mainly elderly population, these findings are not unexpected.

Tolerability

An ocular discomfort study has been performed with the fixed dose combination of brinzolamide/timolol maleate eye drops. The applicant sought to demonstrate superiority of AZARGA over Cosopt in terms of ocular discomfort.

Ocular discomfort (based on burning and stinging, a feeling of heat or warmth, sharp pain or smarting pain; rated on a 5-point scale) was the primary efficacy variable in the Comfort Study, C-05-49. The objective was to compare the comfort of the 2 formulations using the same scale and design as previous studies comparing Azopt and Trusopt (studies C-96-29 and C-96-40, provided in the MAA for Azopt). Study C-05-49 was powered to detect a difference of 0.7 units in mean ocular discomfort scores between the treatment groups AZARGA and Cosopt. Ocular comfort is likely to influence patient compliance and 7 days was chosen based on historical considerations (i.e., previous experience with Azopt).
The ocular comfort was further evaluated through a review of treatment related adverse-events. Patients treated with Cosopt reported a higher incidence of eye pain and irritation that patients treated with AZARGA:

Ocular Comfort/Discomfort-Related Adverse Reactions
C-05-49 (Safety Data)

Adverse Event	AZARGA N = 48		Cosopt N = 47	
	N	%	N	%
Eye Disorders				
Eye pain	5	10.4	11	23.4
Eye irritation	4	8.3	8	17.0
Dry eye	1	2.1		
Photophobia	1	2.1		
Lacrimation increased			2	4.3

In studies C-05-24 and C-05-10 the treatment related adverse reaction pattern is similar:

Ocular Comfort/Discomfort-Related Adverse Reactions
(C-05-10, C-05-24)

	AZARGA (N = 394)	Cosopt (N = 217)	AZOPT (N = 174)	Timolol (N = 175)
Eye pain [a]	8 (2.0%)	14 (6.5%)	1 (0.6%)	2 (1.1%)
Eye irritation [b]	11 (2.8%)	23 (10.6%)	2 (1.1%)	6 (3.4%)
Foreign body sensation [c]	4 (1.0%)	1 (0.5%)	1 (0.6%)	1 (0.6%)
Eye pruritus [d]	3 (0.8%)	1 (0.5%)	1 (0.6%)	-

AZARGA - C-05-10 (12-month study) and C-05-24 (6-month study) combined
Cosopt - This treatment group was included in protocol C-05-10 only
AZOPT - This treatment group was included in protocol C-05-24 only
Timolol - This treatment group was included in protocol C-05-24 only
[a] Comparison of AZARGA and Cosopt treatment groups: p = 0.0050 from chi-square test
[b] Comparison of AZARGA and Cosopt treatment groups: p < 0.0001 from chi-square test
[c] Comparison of AZARGA and Cosopt treatment groups: p = 0.6604 from Fisher's exact test
[d] Comparison of AZARGA and Cosopt treatment groups: p = 1.0000 from Fisher's exact test

The applicant has to a reasonable degree justified the design and analysis of the primary comfort study C-05-49. This design has previously been accepted in other marketing authorization studies.
Additionally, supportive analyses from the pivotal studies are offered. The ocular discomfort adverse event related reactions in studies C-05-24 and C-05-10 support the claim of better tolerability of AZARGA as compared to Cosopt. A randomised double-blind controlled cross-over study of patients´ preference showed a clear preference for AZARGA as well as lower overall discomfort scores as higher frequency of patients with a discomfort score of 0.
In summary, the applicant has justified the claim of overall better tolerability for AZARGA as compared to Cosopt.

Laboratory findings
No clinically significant findings were revealed

Analyses of vital signs, physical findings and other observations related to safety for the Phase III Open-Angle Glaucoma or Ocular Hypertension studies (C-05-10 and C-05-24), which included visual acuity (best-corrected logMAR), ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens), visual fields, pachymetry, dilated fundus parameters (vitreous, retina/macula/choroid, optic nerve including cup/disc ratio), and cardiovascular parameters (pulse and blood pressure) were performed. No treatment group differences were seen for parameters such as corneal thickness, visual field and ocular sign parameters.

A slightly higher proportion of patients treated with AZARGA showed clinically relevant changes from baseline in visual acuity parameters (4.6% AZARGA vs 3.7% Cosopt, 1.7% Azopt and 2.3% Timolol), dilated fundus parameters retina/macula 1.6% AZARGA vs 0.5% Cosopt , 0.6% timolol), and in cup/disc ratio (3.3% AZARGA vs 2.3% Cosopt, 1.1% Azopt, 1.7% timolol). However, most of these changes were considered not treatment related and do not constitute a safety concern.

No statistically significant differences for any of the cardiovascular parameters pulse ratio, systolic and diastolic blood pressure among treatment groups containing beta-blocking agents. Mean reductions in pulse ratio in the AZARGA group ranged from 1.8 to 3.7 bpm. Mean reductions in systolic blood pressure ranged from 1.2 to 4.3 mmHg while mean reductions in diastolic blood pressure ranged from 0.7 to 1.6mmHg. These changes were in line with those seen in patients treated with Cosopt and were considered of no clinical relevance.

Safety in special populations
A total of 960 patients participated in the Open-Angle Glaucoma or Ocular Hypertension studies, including 487 adult patients (18 to 64 years) (50.7%), 473 elderly patients (65 years and older) (49.3%). The conclusions based upon a review of adverse events in the elderly population are consistent with those drawn from the review of the overall safety population. As compared to adults, a higher incidence of blurred vision (4.8% vs 2.2%), visual field defect (4.3% vs 2.2%), cataract (3.4% vs <2%) and hypertension (5.3% vs <2%) were seen. Most of these would be expected in an elderly population and thus are not considered a safety concern. However, the increased incidence of blurred vision might not be explained solely by the age, but a different or more stringent precautionary statement in the SPC to that stated for adults in SPC Section 4.7 was not deemed necessary.

A review analysing safety for the demographic subpopulations age, gender, race, iris colour and other intrinsic factors such as concomitant diseases and medications did not reveal any specific concerns.

Safety related to drug-drug interactions and other interactions
No interaction studies have been conducted, as also mentioned in the SPC.

Discontinuation due to Adverse events
A number of 24 patients were withdrawn because of treatment related adverse events, distributed with 9 patients in patients treated with AZARGA, 9 patients treated with Cosopt, 2 patients treated with brinzolamide, and 4 patients treated with timolol. In the 9 AZARGA treated patients the reasons were:
Allergic conjunctivitis, allergic blepharitis, anterior chamber flare, blurred vision, erythema of eyelid, eye pruritus, eye irritation, foreign body sensation in eyes, ocular hyperaemia, and pharyngolaryngeal pain.
Overall, these reports are not worrying.

Overall conclusions on clinical safety
The safety pattern of the brinzolamide/timolol combination is in consistency with that of the well-known active constituents, and no hitherto unidentified adverse events were revealed with the combination.

The most frequently observed topical adverse events were blurred vision, eye irritation, eye pain and foreign body sensation, each of which were reported with a frequency below 7 %. The withdrawal rate because of adverse events with the fixed combination was low, i.e. 3.8 %.

Overall, the safety profile is not concerning.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan.

The Summary Table:

Safety Concern	**Proposed Pharmacovigilance Activities**	**Proposed Risk Minimisation Activities**
Respiratory disorders (identified)	• routine pharmacovigilance • no additional activity is proposed at this time	Routine risk minimisation. The SPC is up to date. Section 4.3 (Contraindications) includes: • "Bronchial asthma, a history of bronchial asthma or severe chronic obstructive pulmonary disease. • Severe allergic rhinitis and bronchial hyper reactivity" Section 4.4 (Special warnings and special precautions for use) includes the statement: "Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta adrenergic blocking agents may occur. … Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of timolol maleate".
Cardiovascular disorders (identified)	As above.	Routine risk minimisation. The SPC is up to date. Section 4.3 (Contraindications) includes: "Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock." Section 4.4 (Special warnings and special precautions for use) includes the statement: " Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta adrenergic blocking agents may occur. Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of timolol maleate. … They may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, severe peripheral and central circulatory disorders and

		hypotension". Section 4.5 (Interactions with other medicinal products and other forms of interaction) includes the statement: "There is a potential for addictive effects resulting in hypertension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, guanethidine or beta adrenergic blocking agents, antiarrhytmics, digitalis glycosides or parasympathomimetics. The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta adrenergic blocking agents."
Corneal decompensation (identified)	As above.	Routine risk minimisation. The SPC is up to date. Section 4.4 (Special warnings and special precautions for use) includes the statement: "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. Careful monitoring of patients with compromised corneas such as patients with diabetes mellitus or corneal dystrophies is recommended."
Metabolic acidosis reactions (identified)	As above.	Routine risk minimisation. The SPC is up to date. Section 4.2 (Posology and method of administration) includes the statement: "Brinzolamide 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. AZARGA is therefore contraindicated in patients with severe renal impairment (see section 4.3)." Section 4.3 (Contraindications) includes: • "Hyperchloraemic acidosis • Severe renal impairment." Section 4.4 (Special warnings and special precautions for use) includes the statement: "AZARGA contains brinzolamide, a sulphonamide. The same types of undesirable effects that are attributable to sulphonamides may occur with topical administration. Acid-based disturbances have been reported with oral carbonic anhydrase inhibitors. If signs of serious reactions or hypersensitivity occur, discontinue the use of medicinal product."

		Section 4.5 (Interactions with other medicinal products and other forms of interaction) includes the statement: "AZARGA contains brinzolamide, a carbonic anhydrase inhibitor and, although administrated topically, is absorbed systematically. Acid-based disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions must be considered in patients receiving AZARGA." Section 4.8 (Undesirable effects) includes the statement: "AZARGA contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects that are attributable to oral carbonic anhydrase inhibitors may occur with topical administration." Section 4.9 (Overdose) includes the statement: "If overdose with AZARGA eye drops occurs treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored."
Long term use of preserved eye drops (potential)	As above.	Routine risk minimisation. The SPC is up to date. Section 4.4 (Special warnings and special precautions for use) includes the statement: "Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since AZARGA contains benzalkonium chloride, close monitoring is required with frequent or prolonged use."

Important missing information	**Proposed Pharmacovigilance Activities**	**Proposed Risk Minimisation Activities**
Use in children and in pregnancy	As above.	Routine risk minimisation. The SPC is up to date. Section 4.2 (Posology and method of administration) includes the statement: "Paediatric patients AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy." Section 4.6 (Pregnancy and lactation) includes the statement: "There are no adequate data from the use if brinzolamide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for human us unknown.

		Well controlled epidemiological studies with systemic use of beta adrenergic blocking agents did not indicate malformative effects, but some pharmacological effects such as bradycardia have been observed in foetuses or neonates. Data on a limited number of exposed pregnancies indicate no adverse effects of timolol in eye drops on pregnancy or on the health of foetus/newborn child but bradycardia and arrhythmia have been reported in one case in the foetus of a woman treated with timolol eye drops. To date, no other relevant epidemiological data are available. AZARGA should not be use during pregnancy unless clearly necessary."

Medication errors	**Proposed Pharmacovigilance Activities**	**Proposed Risk Minimisation Activities**
	As above.	Routine risk minimisation. The SPC is up to date. Section 4.2 (Posology and method of administration) includes some instructions for appropriate use of product: "If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Method of administration: For ocular use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle, Instruct patients to keep the bottle tightly closed when not in use."

The RMP documentation is in accordance with the EU requirements.

A proper discussion of the existing database and its limitations is provided. In general, these limitations have been reflected in the proposed SPC.

According to the applicant, no specific safety signal has been detected from animal or human data, apart from those already known to be associated to each components of combination: brinzolamide and timolol. Thus, there is no evidence to support the need for specific pharmacovigilance actions.

The MAH will conduct routine pharmacovigilance monitoring for AZARGA. Alcon's routine pharmacovigilance monitoring practices include:

1) Spontaneous Reporting: All cases are thoroughly analysed and particular effort will be placed in the follow up of events that may indicate the following issues: respiratory reactions, cardiovascular reactions, corneal events, metabolic acidosis reactions and long term use of preserved eye drops

2) Reporting of safety data for regulatory authorities: Expedited adverse drug reaction (ADR) reports, Periodic Safety Update Reports (PSURs), and Update of the Risk Management plan (RMP)
3) Continuous monitoring of the safety profile of approved products including: ongoing review of spontaneous reports, signal detection, updating of product information, evaluation of the Risk Management Plan, liaison with regulatory authorities, ongoing review of literature, and other activities required by local regulations.

There are no data in the pediatric population with this fixed combination. This is considered as missing information, and has been added to the relevant sections of the EU-RMP. No specific actions other than routine pharmacovigilance are planned in order to gather more information on efficacy and safety in the paediatric population.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

AZARGA is a fixed dose combination of brinzolamide 10 mg/ml plus timolol 5 mg/ml intended to decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Both active ingredients, used as monotherapy or as unfixed combination, are well known in terms of efficacy and safety for this indication. Thus, the rationale for developing the fixed combination was reasonable.

Efficacy

The existence of a FD combination of brinzolamide and timolol is considered justified according to the Guideline on fixed combination medicinal products based on valid therapeutic principles. A simplification of therapy which improves patient compliance, a known factor of possible improvement in IOP control, further supports the advantages of this fixed combination.

The benefit of the concomitant administration of brinzolamide plus timolol was demonstrated at the time of gaining the marketing authorisation for Azopt. The clinical development programme was aimed to support the benefit of the fixed dose combination of brinzolamide/timolol eye drops, solution with a well designed programme that documents the contribution of elements within the combination as well as comparative benefit over a reference treatment. AZARGA produces greater mean IOP reductions than those produced by either brinzolamide or timolol alone. Also, the non-inferiority of the fixed combination over the currently marketed fixed dose combination of another carbonic anhydrase inhibitor and timolol (Cosopt) was demonstrated. Mean IOP reductions from baseline for AZARGA were clinically relevant and statistically significant at all measurement times. The IOP reduction ranged from -7.2 to -9.2 mmHg for AZARGA and from -7.7 to -8.8 mmHg for Cosopt in the per protocol analysis. In the subset of patients with a screening IOP $\geq$ 22 mmHg and one or more pre study IOP lowering medication, mean IOP observed at 6 months was, in study C-05-10 (N=71), 19.8 mmHg at 8 am and 18.4 mmHg and 10 am; and in study C-05-24 (N= 53) 20.1 mmHg at 8 am and 19.2 mmHg and 10 am.
Therefore, the efficacy requirements for a fixed dose combination therapy have been demonstrated.

Safety

Overall, the safety profile of the fixed combination of brinzolamide/timolol eye drops is similar to that seen with the concomitant use of dorzolamide plus timolol and does not significantly differ from the safety profile of either agent used as monotherapy. A higher incidence of burning and stinging was reported in patients treated with Cosopt as compared to AZARGA.. No unexpected safety concerns have arisen during the development of the fixed dose combination of brinzolamide/timolol. Therefore, it can be concluded that AZARGA is well-tolerated and safe for the use in the treatment of patients with open-angle glaucoma or ocular hypertension.

Risk-benefit assessment

Benefits

Clinical studies aiming to demonstrate the effect of AZARGA in terms of absolute IOP-decreasing properties and non-inferiority to the relevant active comparator, Cosopt, have been submitted.

The obtained results for the fixed combination of brinzolamide + timolol eye drops show a clinically and statistically superior effect to the single components in reducing the IOP in this 6 months study in patients with open angle glaucoma or ocular hypertension. In the 12 months study, comparing a fixed combination of dorzolamide and timolol, non-inferiority was consistently proven as regards IOP-decreasing properties and in the proportion achieving an IOP-value ≤ 18 mm Hg.

The results of both the pilot and pivotal trials demonstrate the superiority of AZARGA versus either active ingredient alone as well as the non-inferiority when compared to an analogous fixed combination of dorzolamide/timolol.

Although the data confirming the efficacy of AZARGA in the target population of open angle glaucoma or ocular hypertension for whom monotherapy provided insufficient IOP reduction is based on a limited number of patients, namely an ITT population of 124 patients treated with AZARGA, the demonstrated effect is convincing and robust.
For AZARGA in this subset, mean IOP at 6 months was, in study C-05-10 (N=71), 19.8 mmHg at 8 am and 18.4 mmHg and 10 am; and in study C-05-24 (N= 53) 20.1 mmHg at 8 am and 19.2 mmHg and 10 am. Even if the approach of the study programme to some extent is failed, resulting in a limited number of target patients, the provided analyses demonstrate evidence of a clinical efficacy in these patients. With the submitted answer the Applicant has justified that the efficacy in the selected, clinically relevant population is consistent with results for the overall population.

The existence of a fixed dose combination of brinzolamide and timolol is considered justified according to the Guideline on fixed combination medicinal products, and is based on valid therapeutic principles. A simplification of therapy which improves patient compliance, a known factor of possible improvement in IOP control, further supports the advantages of this fixed combination.

Risks

The safety profile of AZARGA is overall not concerning. No new safety issues have appeared with the combined use of the elements in the present dossier.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Balance

The majority of patients were on anti-glaucoma medication prior to study inclusion, which was stopped during an appropriate wash-out period. The Applicant was requested to provide data on the type of previous IOP decreasing medication and efficacy results for the sub-group of patients for whom there is general agreement on being considered insufficient responders (i.e. those with IOP-values ≥22 mm Hg) while on treatment before the wash-out phase.
The Applicant has submitted the requested analyses, and it can be concluded that the efficacy of AZARGA eye drops in the subpopulation with an IOP ≥ 22 mmHg at inclusion and treated with at least one anti-glaucoma medication has been demonstrated.

Although the data confirming the efficacy of AZARGA in the target population of open angle glaucoma or ocular hypertension is based on a limited number of patients, the demonstrated effect is robust. The adjunctive use of brinzolamide and timolol is well established in clinical practice which is also reflected in the therapeutic indication of Azopt. No safety new issues have appeared with the combined use of the elements in the dossier. Although the approach of the study programme to some extent is failed, resulting in a limited number of target patients, the provided analyses contribute evidence of a clinical efficacy in these patients.

The overall B/R of AZARGA is positive provided that the applicant agrees to revise the wording of the indication and commits to perform a number of post authorisation follow- up measures to be reported back to the CHMP within predefined timeframes.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority that the risk-benefit balance of AZARGA in the treatment of elevated intraocular pressure in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction was favourable and therefore recommended the granting of the marketing authorization.