SCIENTIFIC DISCUSSION

1. Introduction

Glaucoma is a group of eye disorders traditionally characterized by progressive damage to the eye, at least partly due to elevated intraocular pressure (IOP). It is the leading cause of irreversible blindness in the world and the second leading cause of vision loss after cataract, which is reversible surgically.

Primary open-angle glaucoma (POAG) is the most common form of glaucoma, accounting for about 60 to 70% of all glaucomas. Both eyes are generally affected, but not necessarily equally. Risk factors for (POAG) are elevated intraocular pressure, advanced age, black race, and family history.

Eyes with POAG develop progressive peripheral visual field loss followed by central field loss, in a characteristic pattern, usually but not always in the presence of elevated IOP (in at least 1/6 of patients with glaucoma, the IOP is in the normal range). There are no anatomic factors that identify eyes that are at risk. There are no symptoms; the disease must be screened for and confirmed on comprehensive ophthalmic examination. Visual field loss cannot be recovered once it has occurred.

Most patients with glaucoma require only medication to control the eye pressure. Sometimes, several medications that complement each other are necessary to reduce the pressure adequately. If these treatments fail or are thought likely to fail, laser or filtration surgery are offered.

Topical medications work either by increasing aqueous outflow (alpha adrenergic agonists, miotics, epinephrine compounds, and prostaglandins) or by decreasing aqueous production (beta adrenergic blockers and carbonic anhydrase inhibitors). Systemic carbonic anhydrase inhibitors also decrease aqueous production.

The treatment regimen for a patient often begins with a topical β-blocker, except in patients with cardiac or pulmonary contraindications. These agents effectively lower IOP, have a long duration of action, which allows QD or BID dosing, and are associated with few ocular side effects. Major side effects are similar to those associated with systemic β-blocker therapy, including worsening of heart failure, bradycardia, heart block, and increased airways resistance.

The topical prostaglandins are increasingly chosen as initial therapy in POAG. These prostaglandin-like drugs lower intraocular pressure by increasing the uveoscleral outflow of aqueous humor. They are very effective in reducing the eye pressure and have the advantage of requiring only once a day administration. Of some concern is the ability of these agents to cause permanent iris color changes, conjunctival hyperemia and lash pigmentation.

The rationale for the development of a topical ocular product that combines a prostaglandin analogue (travoprost) and a β-blocker (timolol) in a single formulation was to provide a product with:
− IOP-lowering efficacy that is greater than either component product alone,
− IOP-lowering efficacy that is similar to the concomitant administration of the component products, and
− convenience of once-daily dosing, thereby promoting better compliance.

Travoprost 40 µg/ml/timolol 5 mg/ml Eye Drops, Solution (travoprost/timolol Eye Drops) is indicated for the: decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

The active components of travoprost/timolol Eye Drops, travoprost and timolol maleate, have each been approved as first line therapeutic agents for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension in the EU. Further, the use of travoprost as adjunctive therapy to timolol in the treatment of open-angle glaucoma or ocular hypertension has been granted during the Marketing Authorisation Applicant for Travatan, based on the demonstration of the additional benefit obtained when adding travoprost to patients with insufficient IOP reduction while on timolol.

2. Quality aspects

Introduction

DuoTrav is formulated as sterile, preserved multidose eye drops containing 40 microgram/ml of travoprost and 5 mg/ml of timolol (as maleate) as active substance.

The other ingredients include benzalkonium chloride, mannitol, trometamol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), boric acid, disodium edetate, hydrochloric acid (to adjust pH), and purified water.

DuoTrav is packed in a syndiotactic polypropylene bottle with a polypropylene dispensing plug and a screw cap. Each bottle is placed in a foil overwrap.

Drug Substance

Travoprost

Travoprost is a prostaglandin analogue isopropyl ester prodrug of the (+)-enantiomer of fluprostenol and it is the active substance of a centrally authorised medicinal product i.e. Travatan (EU/1/01/199/001-2).

Detailed information on quality/control of materials used in the synthesis, as well as on the synthesis itself, has been provided by the way of an active substance master file. No change has been made to the currently registered quality documentation: the active substance master file provided includes the changes implemented to the quality documentation of the already authorised product through type I variations (EMEA/H/C/ 390/I/01-03-04-08) as well as some information specific to the DuoTrav application (additional impurity data and batch analysis data for travoprost used in the development of DuoTrav).

Travoprost is a clear to slightly opalescent, colourless to light yellow oil, which is practically insoluble in water. It is hygroscopic under high humidity conditions, susceptible to degradation by heat and humidity, and it is light sensitive.

- Specification

The active substance specification include test for appearance, identity (IR and HPLC), assay (HPLC), optical rotation, impurities (HPLC), residual solvents (GC) and water content.
Batch analysis data provided for 6 recent batches confirm satisfactory compliance and uniformity with the proposed specification.

- Stability of the Product

The re-test period proposed is acceptable according to the stability data submitted and it is identical to the current approved for Travatan.

Timolol (as maleate)

Timolol is decribed in the European Pharmacopoeia. It is a white or almost white, crystalline powder or colourless crystals, soluble in water and in alcohol.

A certificate of suitability of the Monograph of the European Pharmacopoeia monograph (CEP), which includes additional tests and specifications for impurities and residual solvents has been presented by the manufacturer together with a statement certifying that the manufacturing process has not been modified since granting of the CEP by the European Directorate for Quality of Medicines (EDQM).

With regards to related substances, the active is controlled using the TLC test described in the PhEur monograph as well as using a validated HPLC method.

Batch analysis data provided demonstrate compliance with the PhEur Monograph, the additional specifications of the CEP and the additional impurity limits.

- Stability of the Product

Under normal conditions (25°C±2°C/60%±5% RH – intended packaging) and under accelerated conditions (40°C±2°C /75%±5% RH - intended packaging), respectively up to 3-year stability data and 6-month stability data have been provided. The parameter tested included appearance, assay and impurities.
The proposed retest period is supported by the presented data when timolol maleate is stored in a polyethylene bag placed in an aluminium laminated bag.

Drug Product

- Pharmaceutical Development

The objective of the development was to develop a safe, efficacious, stable, comfortable and preserved eye drop formulation. It has been based on already authorised EU formulations containing the individual actives and the same concentration of travoprost and timolol maleate is used.

The supply of travoprost as oil implied the necessity of a surfactant (polyoxyl hydrogenated castor oil 40) in the formulation as a solubilising agent.

The excipients selection has been based on those used in the Travatan formulation: trometamol/boric acid/mannitol as a buffer system, mannitol as a tonicity agent, benzalkonium chloride/boric acid/disodium edetate as a preservative system, trometamol/hydrochloric acid as pH adjuster.

The preservative system showed satisfactory antimicrobial efficacy, which has been demonstrated according to Ph Eur.

All the excipients are Ph Eur quality except polyoxyl hydrogenated castor oil 40 (Polyoxyl HCO 40), which is satisfactorily controlled according to a different standard. Regarding the TSE risk, DuoTrav does not include any component of ruminant origin.

The primary packaging consists of an opaque white oval bottle made of syndiotactic polypropylene with a natural polypropylene dispensing plug and a white polypropylene cap. The bottle is placed in a foil over-wrap. The packaging materials meet the PhEur requirements and they are the same as those approved for Travatan with exception of a colorant i.e. titanium dioxide added to the bottle. The potential extractables and leachables arising from the packaging components including the label and adhesive have been well characterised and satisfactory limits have been included in the finished product specification.

The manufacturing process is based on the one approved for Travatan with the exception of timolol maleate being added with the other water soluble ingredients. The choice of sterilisation by filtration is justified because terminal sterilisation led to deformation of the packaging components and to unacceptable degradation of travoprost.

The formulation used in clinical trials is the same as the one intended for marketing.

- Manufacture of the Product

The manufacturing process involves the following operations: dissolution of water soluble ingredients, preparation and addition of travoprost stock solution, sterile filtration and aseptic filling.

Acceptable specification and retest period has been defined for travoprost stock solution intermediate based on stability data. The maximum holding time for the sterile solution before filling has been adequately justified.
Satisfactory validation data have been provided. All batches comply with the release specification and the results support the reproducibility of the manufacturing process.

- Product Specification

The product specification includes tests for travoprost identity (HPLC and TLC), travoprost assay and degradation products, timolol identity (HPLC and TLC), timolol assay and degradation products, unrelated impurities, benzalkonium chloride identity and assay, boric acid identity and assay, disodium edetate identity, and assay, pH, osmolality, appearance, colour, clarity (PhEur), particles, sterility and fill volume.

Batch analysis data provided for production batches meet the specification at the time of release and confirm the robustness and reproducibility of the manufacturing process.

- Stability of the Product

Stability data have been provided for three primary stability batches. The parameters tested included travoprost assay and degradation products, timolol assay and degradation products, unrelated impurities, benzalkonium chloride assay, boric acid assay, disodium edetate assay, pH, osmolality appearance, colour (PhEur), particles, precipitate, weight change, package condition, sterility and preservative effectiveness.

Under accelerated conditions (40°C/25% RH – commercial packaging) and long-term conditions (25°C/40% RH - commercial packaging) respectively 6-month and 30-month data have been provided.

No significant changes have been observed and the results presented support the proposed shelf-life in-use and storage conditions defined in the Summary of product characteristics (SPC).

An in-use stability study on two production batches has been performed and support the proposed shelf-life defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of unresolved quality issues without impact on the clinical efficacy or safety of the product, therefore the applicant made a commitment to resolve these as post-opinion follow-up measures

3. Non-clinical aspects

Introduction

Pharmacology
The applicant has submitted a number of *in vitro* and *in vivo* studies concerning travoprost and timolol nonclinical pharmacology.

- Primary & secondary pharmacodynamics

F-prostaglandin agonists increase aqueous humor outflow through the uveoscleral pathway in animal models and man. For *in vitro* test systems, 0.1 nM to 100 μM of AL-5848, the free acid of travoprost, was used because of the likely lack of esterase in the test systems to hydrolyze the parent compound

used. Prostanoid receptor binding affinity tests with the free acid of travoprost AL-5848, showed that it is a selective and full agonist at the FP prostanoid receptor. AL-5848 exhibited no significant receptor activity for a battery of 32 physiologically relevant receptors at concentrations of up to 100 μM. *In vivo*, travoprost significantly reduced IOP in lasered monkey. The IOP response was sustained through 24 hours and returned to baseline by 48 hours after the last once daily instillation. Travoprost also lowered IOP in normotensive guinea pig eyes.

Timolol is a well-known nonselective beta-$_1$ and beta-$_2$ adrenergic receptor antagonist that has been utilized clinically for many years for the reduction of elevated IOP in patients with open-angle glaucoma and ocular hypertension. The reduction in IOP is believed to be produced by decreased aqueous humor formation following blockade of the beta adrenoceptors on the non-pigmented epithelial cells of the ciliary body and thereby inhibition of the increased synthesis of cyclic AMP. Beta-adrenoceptors and membrane bound adenylate cyclase have been shown to be present in iris ciliary body and ciliary epithelium in several species. Timolol effectively reduced IOP and aqueous humor formation in rabbits, cats and monkeys. Timolol did not inhibit renin activity or platelet aggregation (up to 1 mg/ml) and showed no fibrinolytic action (up to 1 mg/ml).

Travoprost increased optic nerve head blood flow, which is considered to be a possible component in the etiology of glaucoma, and produced no significant changes in the the electroretinogram (ERG) of Dutch-belted rabbits. Travoprost is approximately 2 times more potent than $PGF_{2\alpha}$ and 10 times more potent than latanoprost for producing miosis in cats however miosis has not been observed in humans dosed with any of the marketed prostaglandin analogues for glaucoma.

Although no nonclinical studies comparing the combination and the individual active ingredients were performed to investigate the potential pharmacodynamic interactions, data from clinical studies showed that the IOP-lowering activity of the combination could be the result of an additive, rather than a synergistic, effect, as a result of the addition of the two distinct mechanisms of action. Furthermore, nonclinical and clinical studies performed with the combination do not suggest a potentiating effect on adverse effects.

- Safety pharmacology programme

Travoprost produced no significant effects on the central nervous, renal or respiratory system. Furthermore, travosprost showed no significant effects on cardiac repolarisation. At high doses, significant effects on cardiac contractility, blood pressure and left ventricular pressure were observed in dogs. However, these effects were observed at plasma concentrations higher than those achieved clinically at IOP-lowering doses, with a wide safety margin. Smooth muscles of the gastrointestinal (GI) tract are contracted by prostaglandin $F_{2\alpha}$; travoprost increases gastrointestinal propulsion in a dose-dependent manner in mice, consistent with the known agonist activity of AL-5848 on FP prostanoid receptors. GI effects are not expected at clinically relevant doses. Prostaglandins are recognized effectors of uterine function. AL-5848 induced concentration-dependent contractions in isolated rat uterine strips, consistent with the known pharmacology of $PGF_{2\alpha}$, with at least a 6-fold safety margin in a worst-case approach.

As with any beta-adrenergic receptor blocking agent, adverse respiratory and cardiac reactions may occur with timolol. Timolol reduces the positive inotropic and chronotropic responses of myocardial tissue and may antagonize beta-adrenoceptors in the bronchi and bronchioles. Furthermore, central nervous system related symptoms could occur; appearing when timolol is discontinued.

The potential interaction of the active ingredients travoprost and timolol was discussed further. Considering that travoprost and timolol are two distinct pharmacological agents, which act by different mechanisms of action and the lack of interaction reports in the literature, support the view that the two agents do not impact significantly on the pharmacodynamics of one another. Low plasma levels and rapid removal of the free acid of travoprost argues against a significant pharmacological interaction occurring between these two mechanistically distinct agents. Furthermore, no signs of ocular or systemic toxicity were observed in toxicology studies conducted in rabbits and monkeys after chronic administration. In conclusion, these data suggest that the individual agents dosed at the clinical concentrations and intended regimen do not interact pharmacologically.

- Pharmacodynamic drug interactions

Travoprost is unlikely to interact adversely with other glaucoma agents or with other receptor-mediated pharmacologic agents. Drug interactions of timolol are typical of nonselective beta adrenergic antagonists and are well defined in the scientific literature.

Pharmacokinetics

Following subcutaneous administration, maximal plasma concentrations and exposure to AL-5848 increased in a dose-proportional manner. Plasma concentrations of AL-5848 declined rapidly and in a biphasic manner following intravenous administration. Timolol is rapidly absorbed following single topical ocular doses reaching maximum concentrations in aqueous humor and plasma 30 minutes after dosing.

In vitro binding of AL-5848 to human, rat and monkey plasma proteins is ≈80%. Tissue distribution studies of travoprost in rats showed highest concentrations in kidney, liver, lung and plasma. Radioactivity concentrations decreased over the first hours, but were still detectable in most tissue through 72 hours after multiple dose regimen. In pregnant rats, radioactivity was measured in amniotic fluid and fetal tissues with highest fetal tissue concentrations in liver and lung. Timolol distributes extensively in rat tissues with highest levels in liver, small intestine, kidney and lung, and lower concentrations in plasma, heart, skeletal muscle and stomach. Following topical ocular administration of travoprost 40 µg/ml/timolol 5 mg/ml eye drops solution, ocular uptake and low systemic exposure in plasma for both AL-5848 and timolol from the combination were observed. Comparison of the data from individual and concomitant administration showed similar pharmacokinetics, but some differences were apparent for timolol.

In vivo and *in vitro*, travoprost is rapidly de-esterified to AL-5848 by plasma esterases. AL-5848, the active acid metabolite of travoprost, is extensively metabolized by the same well-established enzymatic pathways involved in the metabolism of endogenous prostaglandin-F2α. The applicant has established the metabolic profiles and identified the majority of metabolites in rats and monkeys. The metabolism of timolol has been well characterized in rats, mice, and humans in published literature. These studies show that the primary biotransformation products of timolol are identical in rats, mice and humans.

In rats, travoprost is rapidly excreted, with 34% and 61% being recovered in urine and faeces, respectively. Travoprost undergoes extensive biliary excretion and is excreted in the milk of lactating rats. The pattern of excretion of timolol is similar in rats and dogs, with the majority of the dose excreted in urine (58 and 68% respectively) and the remainder recovered in urine (26 and 19% respectively).

Concomitant topical ocular administration of travoprost and timolol to rabbits showed no significant changes in pharmacokinetics of AL-5848 compared with those seen for the individual drugs. Exposure to timolol was significantly reduced in the combination compared to that of the individual drug. The applicant acknowledges the trend towards lower timolol concentrations in ocular tissues with the use of the travoprost/timolol combination product compared to the timolol active ingredient and attributes these differences to the variability of the data.

Potential pharmacokinetic interactions between active ingredients are unlikely, since travosprost and timolol undergo different metabolic pathways and also taking into account the low systemic levels achieved following topical ocular administration.

Toxicology

Travoprost and timolol have been evaluated in a variety of toxicology studies in laboratory animals and *in vitro* test systems.

- Single dose toxicity

The oral LD50 for timolol maleate is 1028 mg/kg in rats and 1137 mg/kg in mice, comparable to that of other beta-adrenergic receptor antagonists.

An ocular irritation test was conducted with the combination travoprost/timolol in rabbits. This single-dose toxicity study in rabbits was an exploratory screening study to assess ocular safety of 40 µg/ml travoprost / 5 mg/ml timolol (FID 102872 marketed formulation) in an exaggerated dosing paradigm. Three rabbits were assigned to the test group and one eye of each animal selected for use. The formulation was administered as two drops to the right eye every 30 minutes for a total of 10 doses. Immediately following the first and last dose, a comfort evaluation was performed. One hour after the last dose, the test eye was examined biomicroscopically.

Findings consisted of moderate conjunctival congestion (score=2) on a 0-3 point scale in all animals and a single animal was observed to have minimal discharge (score=1) on a 0-3 point scale. Two out of three animals had minimal discomfort (score=1) on a 0-4 point scale after the first dose and 3/3 animals had minimal discomfort after the last dose.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose topical ocular studies conducted with travoprost in rabbits (6 months, up to 0.01%) and cynomolgus monkeys (1 year, up to 0.012%) showed no signs of ocular irritation or systemic toxicity. Plasma C_{max}, local and systemic exposure achieved in these animal species with regard to the dose regimen was higher than those in man. There was an increase in iris pigmentation and a widened palpebral fissure in the 1-year monkey study, as has been noted in primates with other prostanoids. In the rat, subcutaneous administration of 30 and 100 µg/kg for 6 months showed hyperostosis and fibrosis of bones (femur and sternum). Bone changes were considered responsible for the extramedullary hematopoiesis in the liver and spleen, and decreases in red blood cell parameters observed. This effect is not observed in mice, rabbits or monkeys, and was apparent at doses >200 times those proposed in clinical practice.

Timolol gelable drops (up to 1%) was administered by the topical ocular route to rabbits (1 and 3 months) and cynomolgus monkeys (1 year). There were no signs of ocular toxicity observed in the rabbit studies and no signs of ocular or systemic toxicity observed in the monkeys. A review of the ocular studies conducted with timolol in rabbits and dogs showed no treatment-related observations except some cardiovascular changes in the dog. Since ocular administration achieves low systemic exposure, there are acceptable margins of safety. Two repeat-dose topical ocular studies were conducted in rabbits and one was conducted in monkeys with the travoprost/timolol combination. No signs of ocular irritation or ocular/systemic toxicity at doses of up to 200 µg/ml travoprost / 5 mg/ml timolol were observed in rabbits. Increased iris/ciliary body pigmentation along with widening of the palpebral fissure was observed in monkeys, consistent with those findings previously observed with travoprost.

Toxicokinetic studies were performed following topical ocular administration of travoprost/timolol combination in rabbits and monkeys. AL-5848 exposure in animals dosed with the combination test articles showed increasing exposure with increasing travoprost concentration. There was no significant accumulation. The toxicokinetic data show an increase of AL-5848 plasma concentrations when administered together with timolol in rabbits (3 and 9 months studies). This observation could not be confirmed in monkeys, as the toxicokinetic study was perfomed only with the combination travoprost/timolol.

- Genotoxicity

Travoprost has no significant potential for genotoxicity. Timolol has been shown to have low genotoxic potential in a series of *in vitro* and *in vivo* studies.

- Carcinogenicity

Two-year carcinogenicity studies were conducted in the mouse and the rat with travoprost and timolol. There was no significant risk of carcinogenic potential observed with exposure to travoprost or timolol.

- Reproduction Toxicity

Fertility and reproductive performance were not affected by travoprost at doses up to 10 µg/kg/day. Reproductive and developmental toxicity studies in rats and mice demonstrated the uterine effects of travoprost, as it is expected from its pharmacology, characterised by early resorptions, post-implantation loss and reduced foetal weight. The effects were more pronounced in the mouse than in the rat, the no observed effect level (NOEL) for embryo-fetal toxicity being 0.3 and 3 µg/kg/day, respectively.

The use of travoprost in women who are or may become pregnant is contraindicated, as is reflected in the SPC.

In reproduction and fertility studies in rats with timolol, there were no adverse effects on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

- Local tolerance

Travosprost and timolol showed no evidence of sensitization potential.

- Other toxicity studies

The caractogenic potential of travoprost/timolol combination was also investigated by the applicant. Studies conducted in monkeys and rabbits with travoprost, timolol and the travoprost/timolol combination showed no abnormal lenticular findings and therefore there appears to be no concern regarding cataract formation. These results are consistent with observations from clinical trials in humans, as well as PSUR data for both Travatan and timolol, which revealed no relation to the development of cataracts.

The inmunotoxicity of travoprost and timolol was assessed as a part of the chronic toxicology studies; in these studies, travoprost and timolol did not show evidence of any immunotoxic potential. Regarding the fixed combination, results from three topical ocular chronic studies in rabbits and monkeys did not provide evidence of immunotoxicity.

In relation to the allergenic potential, studies conducted with travoprost and timolol in guinea pig were negative for induction of allergenicity. For the combination, chronic topical ocular studies in rabbits and monkeys did not show any sign of allergenic potential.

The impurities AL-12419 (trans isomer of travoprost) and Al- 5848 are classified as qualified on the basis of the following toxicological data:

- Animals have been exposed to the impurity AL-12419 in various toxicology studies up to>100 times the potential patient exposure
- The impurity AL-5848 is at the same time the pharmacologically active free acid of travoprost, and therefore animals have been extensively exposed to AL-5848.

Although the specified and unspecified unrelated impurities (derived from package material or label/adhesive) are observed in very low concentrations (each max. 1.3 ppm, total max. 6.2 ppm) the toxicological relevance of these impurities has been discussed. The toxicological profile of impurities from package and label was tested in a number of studies. All of them were negative for cytotoxicity, incutaneous reactivity, ocular irritation or toxicity. Furthermore, there is no evidence in the literature concerning the potential mutagenicity of the timolol acrylate reaction product. It is found at levels below 1% (ICH limit) and therefore there is no concern about toxicity.

Ecotoxicity/environmental risk assessment

The physico-chemical properties of travosprost and timolol and the predicted concentrations likely to enter the environment do not anticipate an environmental impact.

4. Clinical aspects

Introduction

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 (PK)
The pharmacokinetics of travoprost has not been studied after systemic administration. After oral administration timolol is rapidly and completely absorbed (~90%). Detectable plasma concentrations of timolol are observed within one-half hour and peak concentrations occur 1 to 2 hours post-dose. The apparent elimination $t_{1/2}$ of timolol in plasma is approximately 4 hours and this is essentially unchanged in patients with moderate renal insufficiency. Timolol is partially metabolized by the liver; timolol and its metabolites are excreted by the kidney in animals. Plasma concentrations following oral administration are about half those seen after intravenous administration indicating approximately 50% first-pass metabolism.

The clinical pharmacology programme for travoprost/timolol eye drops, solution, consists of 2 new clinical pharmacokinetics studies (Study C-02-35 and Study C-98-62), aimed to determine plasma concentrations of AL-5848 (active metabolite of Travatan) and timolol, when the combination of travoprost/timolol Eye Drops was administered, compared to when Travatan and timolol 5 mg/ml were administered separately; and to assess the potential for a drug-drug interaction between travoprost and timolol.

Study C-98-62 was conducted to compare the plasma timolol profiles following topical ocular administration of TIMOPTIC 5 mg/ml and 2 extended-release timolol formulations (TIMOPTIC-XE and TIMOLOL GFS). The results from the TIMOPTIC 5 mg/ml group serve as comparison with the timolol plasma pharmacokinetic data from Study C-02-35.

The pharmacokinetic/pharmacodynamic profile of this fixed dose combination is also supported by the results of the studies performed during the clinical development programme of Travatan and by data from the literature for timolol, which are briefly presented below.

- Absorption

Travoprost is well absorbed through the cornea and is rapidly hydrolyzed via esterases to the pharmacologically active acid metabolite AL-5848.

Timolol is well absorbed through the cornea and rapidly distributes into ocular tissues and the systemic circulation following topical ocular administration in animals.

- Distribution

The active metabolite, AL-5848, is present at low concentrations in the systemic circulation. Data from 5 multiple-dose pharmacokinetic studies of travoprost ophthalmic solutions (total 122 subjects) have shown that plasma concentrations of AL-5848 are below 10 pg/ml (the assay limit of quantitation, LOQ) in two-thirds of the subjects. In those individuals with quantifiable plasma concentrations (N = 38), the mean plasma C_{max} was 18 ± 7 pg/ml and was reached within 30 minutes. There were no apparent differences in plasma concentrations between Days 1 and 7, indicating that steady-state pharmacokinetic was reached early and that there was no accumulation. AL-5848 can be measured in human plasma only during the first hours after topical ocular administration. Thereafter, plasma levels declined rapidly to below the 10 pg/ml assay quantitation limit at 1 hour post-dose.

Timolol can be measured in human aqueous humor and plasma for up to 12 hours after topical ocular administration of timolol 5 mg/ml. Timolol is partially metabolized by the liver. Timolol biotransformation pathways include oxidation and hydrolytic cleavage of the morpholine ring, as well as oxidation and cleavage of the oxypropanolamine side chain.

- Elimination

Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of AL-5848 in man could not be determined. Metabolism is the major route of elimination of both travoprost and AL-5848. In humans, less than 2% of the dose was recovered in the urine as AL-5848 following topical ocular administration of travoprost.

The apparent terminal elimination $t_{1/2}$ of timolol in plasma was approximately 4 hours after topical ocular administration of travoprost/timolol Eye Drops or timolol 5 mg/ml. Timolol and its metabolites are primarily excreted in the urine.

The applicant was asked to provide further data to demonstrate whether the excretion of travoprost/timolol is different to that seen for each component given separately. The applicant argued that following topical ocular administration of travoprost/timolol Eye Drops, Solution (study C-02-35), the plasma profiles for both the travoprost free acid (AL-5848) and timolol were similar to those observed for each topical agent when administered alone. Since the systemic exposure for both compounds was unchanged when given together, these findings support the conclusion that the elimination (excretion) pathways of both AL-5848 and timolol are not altered when administered in fixed combination. The answer was considered to be acceptable by the CHMP.

- Special populations

No specific studies with the fixed dose combination have been performed. Data from the studies performed with travoprost have been provided. No clinically relevant changes in laboratory data were observed in patients with impaired (mild to severe) hepatic or renal function. No dosage adjustment is necessary in patients with hepatic or renal impairment based on travoprost (Travatan) data.

No specific pharmacokinetic studies have been performed in patients under 18 years of age. Travatan and timolol Eye Drops are not recommended for use in paediatric patients. Travoprost/timolol Eye Drops is not recommended in patients below the age of 18 years and is stated in section 4.2 of the SPC.

The applicant was also asked to give further information on other subpopulations such as different ethnic groups (different iris colour), patients with aphakia and pseudophakia etc. Data provided by the applicant do not suggest any clinically relevant difference in the efficacy of this fixed dose combination based on age, race, iris colour and diagnosis. Only a consistent, although minor, difference in mean IOP reduction based on gender has been noted, with males showing a slightly higher mean IOP reduction than that for females when administering travoprost plus timolol, both as a fixed or concomitantly used combination. This information was not considered to add relevant information for prescribers and therefore, it was not considered necessary to address this issue in the SPC.

With regard to the information provided in aphakic and pseudoaphakic patients, the applicant considers that the statement proposed for Section 4.4, in accordance to that stated in the SPC approved for Travatan, is appropriate since no definite causality, or lack of causality, for cystoid macular edema (CME) has been demonstrated for prostaglandin analogues in pseudophakic or aphakic eyes. The applicant's proposal was considered to be acceptable by the CHMP.

- Pharmacokinetic interaction studies

No studies evaluating drug-drug interactions have been performed. Since travoprost undergoes a biotransformation pathway similar to endogenous prostaglandin-F2α, and since systemic levels of active metabolite following topical ocular administration are negligible, interactions with concomitant medications in patients receiving topical ocular doses is considered to be unlikely. *In vitro* experiments have shown travoprost free acid to be moderately bound (about 80%) to plasma proteins in humans, indicating drug-drug interactions through protein binding to be unlikely.

Specific drug interaction studies with cytochrome P450 substrates have not been conducted with AL-5848. The very low systemic exposure to AL-5848 after topical ocular administration of travoprost would not influence the P450 enzyme-mediated metabolism of other concomitant agents. Concomitant

administration of potent inhibitors of cytochrome P450 enzymes would not impact the low systemic exposure of AL-5848 after topical ocular administration of travoprost/timolol Eye Drops, since travoprost is metabolized extensively by routes other than cytochrome P450 pathways.
Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during co-administration of oral timolol with quinidine, possibly because of quinidine inhibiting the metabolism of timolol by the cytochrome P450 CYP2D6

Study C-02-35, a single centre, double-masked, randomised, 3-way cross-over, multiple-dose pharmacokinetic study, was aimed to determine plasma concentrations of AL-5848 following the administration of the fixed dose combination of travoprost/timolol eye drops as compared to those of travoprost and timolol given separately. Fifteen healthy volunteers (from 19 to 79 year old) participated in study. Plasma concentrations of AL-5848 and of timolol were measured. The results show that only 18 plasma samples (4 out of 15 subjects) following dosing with either travoprost/timolol eye drops or Travatan had quantifiable concentrations of AL-5848 (LOQ<10 pg/ml). The applicant concludes that no differences between treatment groups were identified and that it can be concluded that travoprost/timolol eye drops and Travatan, both dosed once daily for 3 days, result in similar plasma concentrations of AL5848. However, from such limited data it appears difficult to conclude on bioequivalence. Nevertheless, the difficulties in performing such an analysis are recognised due to the limited systemic exposure of AL-5848 and thus, no further studies were considered necessary.

The systemic absorption of timolol was also determined. The mean peak plasma concentrations on Day 1 were 0.552 ng/ml after travoprost/timolol Eye Drops and 0.482 ng/ml after timolol 5 mg/ml. At steady-state (Day 3), the mean peak plasma concentrations were 0.692 ng/ml and 0.613 ng/ml following travoprost/timolol Eye Drops and timolol 5 mg/ml, respectively. C_{max}, T_{max} and AUC_{0-12} for timolol showed no statistically significant differences between treatments. The applicant concludes on the bioequivalence of the plasma concentrations of timolol after travoprost/timolol eye drops compared to timolol in monotherapy based on the lack of statistically significant differences.

Further, an analysis of the ratios of the geometric means for C_{max}, AUC_{0-12} and AUC_{0-inf} were evaluated. The upper bounds of the 90% confidence interval for the ratios of the geometric means exceed the 125% criteria. However, due to the lack of statistical difference between the geometric means, the high level of inter-subject variability, and the small absolute differences in mean concentration and exposure (mean differences of 0.087 ng/ml in C_{max} and 0.314 ng·h/ml in AUC_{0-12} on Day 3), the width of the confidence interval was not considered to be clinically relevant.

From the results of this study, it is also concluded that administration of travoprost/timolol eye drops did not result in a change in the systemic exposure to either timolol, as compared to timolol 5 mg/ml alone, or travoprost, as compared to Travatan given in monotherapy. Therefore, the lack of drug-drug interaction between timolol and Travatan was concluded.

Pharmacodynamics

- Mechanism of action

No specific pharmacodynamic studies have been performed with the fixed dose combination of travoprost/timolol eye drops.

Travoprost is a highly selective full FP prostanoid receptor agonist that is believed to reduce intraocular pressure by increasing uveoscleral outflow, although the exact mechanism of action is unknown at this time. Reduction of intraocular pressure starts within approximately 2 hours after administration, and the maximum effect is reached after 12 hours. The effect can be maintained for periods exceeding 24 hours with a single dose.

Timolol maleate is a beta-1 and beta-2 adrenergic receptor-blocking agent; when applied topically to the eye, 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 reduced aqueous humour formation, although a slight increase in outflow facility has also been reported.

The proposed fixed dose combination contains the two active components, i.e. travoprost and timolol maleate. Since they are known to have different mechanism of actions, it is foreseen that a combined effect would result in additional IOP reduction compared to either compound administered alone.

- Primary and Secondary pharmacology

No specific pharmacodynamic studies have been performed with the fixed dose combination of travoprost/timolol eye drops.

Clinical efficacy

The clinical development plan to demonstrate the safety and efficacy of travoprost 40 µg/ml/timolol 5 mg/ml Eye Drops, Solution (travoprost/timolol Eye Drops) included 5 clinical trials that were multicenter, randomized, double-masked, parallel group, controlled clinical safety and efficacy trials.

There are 2 ongoing efficacy/safety clinical studies (C-04-03 and C-04-04) conducted outside the EU, which compares travoprost/timolol Eye Drops to the concomitant administration of latanoprost and timolol.

Overall, the comments from the regulatory agencies (Sweden, UK and Spain) have been followed during the clinical development programme of this fixed dose combination for travoprost and timolol.

- Dose response studies

The proposed dosage for travoprost/timolol Eye Drops, i.e. travoprost 40 µg/ml plus timolol 5 mg/ml, is mainly based on the combination of currently approved doses for both products.

Although timolol has been dosed according to the SPC recommendation, the proposed fixed dose combination of travoprost/timolol does not allow the maximum dose of timolol, i.e. one drop 0.5% twice daily, to be achieved. This maximum dose was used in the clinical study provided with the initial Marketing Authorisation Applicant to support the use of travoprost in addition to timolol in patients with insufficient control on timolol monotherapy.

The applicant argues that the prostaglandin component is believed to provide the largest contribution to the IOP-lowering efficacy of the travoprost/timolol fixed combination because prostaglandin analogues have consistently shown superior efficacy to timolol in clinical trials and that better IOP-lowering efficacy is observed with once-daily dosing of a prostaglandin analogue, and little or no long-term clinical benefit is expected from twice- daily dosing of timolol. The applicant's justification of the selection of a once-daily dosing frequency for the fixed combination travoprost/timolol Eye Drops, Solution was considered to be acceptable.

- Main studies

Five clinical studies were conducted to support the efficacy and safety of the fixed dose combination of travoprost/timolol in the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. These studies were multicenter, randomised, double-masked, parallel group, controlled clinical safety and efficacy trials.

Summary of Safety/Efficacy Trials of Travoprost/Timolol Eye Drops

Study # (Study Type / Location)	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing[a]	No. of Sites[b]	No. Patients Randomized (ratio)	Status
C-02-03 Safety/Efficacy Posology Europe	Randomized, double-masked, parallel group	6 weeks	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • Travoprost/Timolol	• 1 drop AM • 1 drop PM	14	92 (1:1)	Completed
C-01-69 Safety/Efficacy Contribution of Elements US	Randomized, double-masked, parallel group	3 months plus 3 month masked extension	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • TRAVATAN • Timolol	• 1 drop AM • 1 drop PM • 1 drop BID	33	263 (1:1:1)	Completed
C-01-70 Safety/Efficacy Concomitant administration #1 US	Randomized, double-masked, parallel group	3 months plus 3 month masked extension	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • TRAVATAN+Timolol	• 1 drop AM • 1 drop PM + 1 drop AM	19	316 (1:1)	Completed
C-02-41 Safety/Efficacy Concomitant administration #2 US	Randomized, double-masked, parallel group	3 months plus 3 month masked extension	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • TRAVATAN+Timolol • Timolol	• 1 drop AM • 1 drop PM + 1 drop AM • 1 drop BID	26	403 (2:2:1)	Completed
C-02-28 Safety/Efficacy Comparative Europe, Australia, New Zealand, Asia	Randomized, double-masked, parallel group	12 months	Adults, open-angle glaucoma or ocular hypertension	• Travoprost/Timolol • Latanoprost/Timolol (XALACOM)	• 1 drop AM • 1 drop AM	41	408 (1:1)	Completed

Travoprost/Timolol = Travoprost 40 µg/ml/Timolol 5 mg/ml Eye Drops, Solution
TRAVATAN = Travoprost 40 µg/ml Eye Drops, Solution
Timolol = Timolol 5 mg/ml Eye Drops, Solution
Latanoprost/Timolol (XALACOM) = Latanoprost 50 µg/ml/Timolol 5 mg/ml Eye Drops, Solution
Latanoprost = Latanoprost 50 µg/ml Eye Drops, Solution
[a] In each study eye
[b] Number of sites that enrolled patients

METHODS

Study Participants
Inclusion criteria were common across the 5 clinical trials (C-02-03, C-01-69, C-01-70, C-02-41 and C-02-28), with the exception of the IOP entry criteria and response to previous IOP lowering therapy:

- 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.

- At screening, patients were required to discontinue use of all IOP-lowering medications for a minimum period of 5 days (for miotics and oral/topical carbonic anhydrase inhibitors (CAI)), 14 days for alpha and alpha/beta agonist to 28 days (for beta antagonists and prostaglandin analogues). This visit was followed by off-therapy Eligibility 1 and 2 Visits in which patients must have met the following IOP entry criteria 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 to 24 at 8AM (except in Study C-01-69 that required a stringent IOP entry criteria, i.e. from 26 to 36mmHg at 8AM). Patients in C-02-28 had one Eligibility Visit prior to randomization and assignment of study medications.

The off-therapy IOP criteria for entry in Study C-01-69 were selected to identify patients with higher IOP who would be expected to have a greater need for combination therapy. Additionally, the entry criteria for C-02-28 required that patients be intolerant or insufficiently responsive to another IOP-lowering agent. An upper IOP limit of 36 mmHg was chosen for safety reasons for all studies.

Qualifying IOP for Studies C-02-03, C-01-69, C-01-70, C-02-41 and C-02-28

Study	Qualifying IOPs[a] (mmHg)					
	Eligibility Visit 1			Eligibility Visit 2		
	8/9 AM	10/11 AM	4 PM	8/9AM	10/11 AM	4 PM
C-02-03	24 to 36	21 to 36	21 to 36	24 to 36	21 to 36	21 to 36
C-01-69	26 to 36	24 to 36	22 to 36	26 to 36	≤ 36	≤ 36
C-01-70	22 to 36	≤ 36	≤ 36	22 to 36	≤ 36	≤ 36
C-02-41	22 to 36	≤ 36	≤ 36	22 to 36	≤ 36	≤ 36
C-02-28	24 to 36	21 to 36	21 to 36	N.A.	N.A.	N.A.

[a] IOP in the qualifying eye following washout; neither eye could have an IOP > 36 mmHg at any time-point or visit
N.A. = Not Applicable

The exclusion criteria for the 5 clinical trials were similar: patients with history of chronic or recurrent severe inflammatory eye disease or significant or progressive retinal disease, patients with history of ocular trauma (within 6 months), ocular infection (within 3 months), ocular surgery (within 6 months), or laser surgery (within 3 months), best-corrected visual acuity worse than 0.6 logMAR score, cup/disc ratio greater than 0.80, severe central visual field loss in either eye, extreme narrow anterior chamber angle with complete or partial closure, use of contraindicated medications such as glucocorticoids, less than 30 days stable dosing of any medication that may affect IOP, history of chronic respiratory disease and of severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease.

Treatments
The combination of travoprost 40 µg/ml plus timolol 5 mg/ml Eye Drops, Solution (travoprost/timolol Eye Drops) was used in the clinical development plan that included 5 clinical trials to demonstrate the safety and efficacy.

Objectives

Study number	Objective
C-02-03	To compare travoprost/timolol Eye Drops dosed in the morning to travoprost/timolol Eye Drops dosed in the evening
C-01-69	To compare the safety and efficacy of travoprost/timolol Eye Drops dosed once-daily in the morning to Travatan dosed once-daily in the evening and timolol 5 mg/ml Eye Drops dosed twice daily in a contribution-of-elements design
C-01-70 and C-02-41	To compare travoprost/timolol Eye Drops dosed once-daily in the morning to the concomitant administration of Travatan dosed once-daily in the evening plus timolol 5 mg/ml Eye Drops dosed once-daily in the morning
C-02-28	To compare travoprost/timolol Eye Drops to Latanoprost 50 µg/ml/timolol 5 mg/ml Eye Drops, Solution, both dosed once-daily in the morning

Outcomes/endpoints
Primary endpoint: mean IOP at different time points and visits was the primary efficacy parameter.

Secondary endpoints:
- The proportion of patients with IOP less than 18 mmHg at selected or all visits was a secondary variable in order to assess clinical relevance of therapy for individual patients. An IOP of 18 mmHg was used as the 'target IOP' consistent with the findings of the National Eye Institute-sponsored Advanced Glaucoma Intervention Study (AGIS) which demonstrated that patients with IOP < 18 mmHg at all visits over 6 years had mean changes from baseline in visual field score close to zero during follow-up.

- Mean changes 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 3 time-points during the day:
- Studies C-01-69, C-01-70 and C-02-41 were conducted in the **US** and used the time-points 8 AM, 10 AM and 4 PM.
- Studies C-02-03 and C-02-28 were conducted in **Europe and in countries outside the EU**. The time-points used, 9 AM, 11 AM and 4 PM, are standard for European clinical study practice.

Table below summarises the timing of study visits and IOP measurements in the 5 studies.

Visits and IOP Measurement Time-Points by Visit for Studies C-02-03, C-01-69, C-01-70, C-02-41, and C-02-28

Study	Visits								
	Screen	Eligib. 1	Eligib. 2	Week 2	Week 6	Month 3	Month 6	Month 9	Month 12
C-02-03	(X)	X	X	X	X	-	-	-	-
C-01-69	(X)	X	X	X	X	X	X	-	-
C-01-70	(X)	X	X	X	X	X	X	-	-
C-02-41	(X)	X	X	X	X	X	X	-	-
C-02-28	(X)	X	-	X*	X*	X*	X	X*	X

(X) = IOP measurements at the screening visit (Screen) were not required to be taken at a specific time of day and were not used in the analyses
X = IOP measurement – 3 time-points (8/9 AM, 10/11 AM and 4 PM)
X* = IOP measurement – 1 time-point (9 AM)

If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both of a patient's eyes were dosed, the worse evaluable eye was selected for analysis.

In the long-term studies that tested non-inferiority as the primary statistical objective (C-01-70, C-02-41 and C-02-28), a criterion of 1.5 mmHg difference was used, which is considered acceptable and consistent to previous studies.

In the posology study (C-02-03), 2.5 mmHg was selected as the equivalence criterion.

Sample size
See table 'Summary of Safety/Efficacy Trials of travoprost/timolol Eye Drops'

Randomisation
See table 'Summary of Safety/Efficacy Trials of travoprost/timolol Eye Drops'

Statistical methods
If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both of a patient's eyes were dosed, the worse evaluable eye was selected for analysis. Both eyes of a patient were required to be dosed unless there was a safety reason not to do so. The worse eye was defined according to eligibility status as follows: the eye with the higher IOP at 8/9 AM averaged across the eligibility visit(s); if both eyes were equal, then the eye with the higher IOP at 10/11 AM; if both eyes were equal, then the eye with the higher IOP at 4 PM; if both eyes were equal, then the right eye was selected for analysis.

Per protocol (PP) data and intent-to-treat (ITT) 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.

All patients who received study medication and had at least one on-therapy study visit were considered evaluable for the intent-to-treat analysis. All patients who received study medication, had at least one on-therapy study visit and satisfied inclusion/exclusion criteria were considered evaluable for the per protocol analysis. 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. In the long-term studies that tested non-inferiority as the primary statistical objective (C-01-70, C-02-41 and C-02-28), a criterion of 1.5 mmHg difference was used. This criterion is the same as used and accepted in previous regulatory submissions of drug products intended for the reduction of elevated intraocular pressure.

In the posology study (C-02-03), 2.5 mmHg was selected as the equivalence criterion. This criterion was chosen so that, unless there was a substantial difference in efficacy, other factors such as safety, convenience and patient acceptance would guide the preference between morning and evening dosing.

RESULTS

Conduct of the study
All clinical trials with travoprost/timolol were in a randomised, double-blind manner and were according to ICH GCP regulations. The applicant has conducted appropriate audits of the completed clinical studies submitted in this application.

Baseline data
The population included in clinical trials ranged in age from 18 to 91 years, with slightly more female as compared to male patients (57.6% vs. 42.4%), and with a similar distribution of adult and elderly (50.3% vs. 49.7%, respectively) patients.

The majority were Caucasian (75.8%) and had brown irides (50.9%). Overall, no clinically relevant differences were observed between the treatment groups in the assessment of demographic characteristics.

Comorbidity and concomitant medication were those expected for an aging population, with hypertension being the most common systemic disease, seen in almost half of the patients. Concomitant ocular diseases such as cataracts, dry eye and pinguecula were more commonly seen in

the comparative groups (i.e. Travatan plus timolol, timolol, Travatan) as compared to the travoprost/timolol group.

Numbers analysed

Study C-02-03 (Safety/Efficacy Study – Posology)

This study was designed as an equivalence study, with a pre-specified delta limit of equivalence of 2.5 mmHg. Ninety-two patients were randomized to one of 2 treatment groups. One patient was excluded from the intent-to-treat analysis due to exit prior to generating on-treatment data. This resulted in 91 patients in the intent-to-treat data set. A total of 9 patients were excluded from the per protocol analysis due to protocol violations (e.g., non-qualifying IOP, IOP measurement /visit outside study window, inadequate time interval from dosing to IOP measurement, patient did not dose/ran out of medication, inadequate washout, and use of excluded concomitant medication) resulting in 83 patients in the per protocol data set.

Study C-01-69 (Safety/Efficacy Study – Contribution of Elements)

Two hundred and sixty three patients who met IOP criteria were randomly assigned to each of the three treatment groups. Of these, 258 constituted the ITT population. Primary endpoint was mean IOP at 8AM, 10AM and 4 PM in the worst eye at 2-week, 6-week and 3-month visits. Patients were followed for an additional 3-month extension phase in a masked way.

A total of 18 patients were excluded from the per protocol analysis due to protocol violations (e.g., non-qualifying IOP, dosing non-compliance, violation of inclusion/exclusion criteria, and use of excluded concomitant medication) and thus, from the 258 patients evaluable for ITT analysis 245 remained for the PP analysis.

Study C-01-70 and Study C-02-41 (Safety/Efficacy Studies)

Study designs were identical with the exception of a timolol 5 mg/ml twice-daily treatment arm that was included in C-02-41 to allow for internal study validation.

Three hundred sixteen patients were randomized in Study C-01-70 to one of 2 treatments in a 1:1 ratio (travoprost/timolol Eye Drops, Travatan plus timolol 5 mg/ml). All 316 patients were included in the safety analysis, 11 patients were excluded from the intent-to-treat analysis due to exit prior to generating on-treatment data. This resulted in 305 patients in the ITT data set. A total of 23 patients was excluded from the per protocol analysis due to protocol violations resulting in 293 patients in the per protocol data set.

In C-02-41, 403 patients were randomized to one of 3 treatment groups in a 2:2:1 ratio (travoprost/timolol Eye Drops, Travatan plus timolol 5 mg/ml, timolol 5 mg/ml). Two patients were excluded from the intent-to-treat analysis due to exit prior to generating on-treatment data. This resulted in 401 patients in the intent-to-treat data set. A total of 16 patients was excluded from the per protocol analysis due to protocol violations resulting in 387 patients in the per protocol data set.

Study C-02-28 (Safety/Efficacy Study – Comparative)

Four hundred and eight patients were randomized to one of 2 treatment groups. One of these patients was never dosed with study medications, leaving 407 patients evaluable for safety analysis. Of these, 398 were included in the ITT analysis and 332 Per Protocol analysis (due to 76 exclusions for protocol violations). The per protocol data set was the basis for primary inference in this non-inferiority study.

Outcomes and estimation

Study C-02-03 (Safety/Efficacy Study – Posology)

Differences between AM and PM posology were within the 2.5 mmHg delta and thus, equivalence was concluded by the applicant. Nevertheless it is noted that the rationale provided by the applicant for selecting such a broad delta was not considered to be convincing.

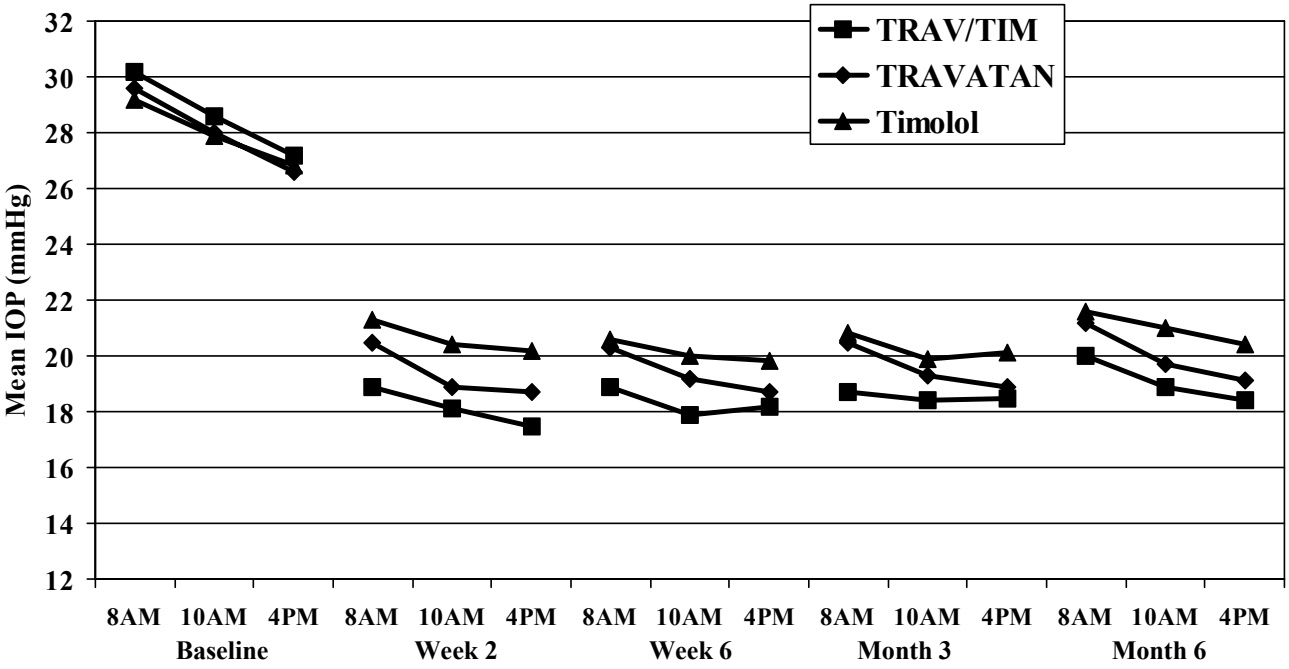
Using a stricter and generally accepted criterion, i.e. a delta of 1.5 mmHg, equivalence can not be concluded at all time-points in each visit. The AM posology, achieved lower mean IOP at 9AM and at 11AM, while at 4PM the PM posology achieved lower IOP values, which is opposed to what it would be expected considering the pharmacokinetic profile of each component. Travoprost/timolol Eye

Drops produces statistically significant reductions from baseline in IOP, with mean reductions ranging from approximately 8 to 10 mm Hg, which means an IOP reduction of 33% to 38% relative to baseline in the per protocol analysis. Considering the pre-established response criteria, (i.e. patients who achieve IOP levels below 18 mm Hg in at least one time-point at each study visit), travoprost/timolol Eye Drops provides IOP control in 63% (AM dosing) and 65% (PM dosing) of patients.

Study C-01-69 (Safety/Efficacy Study – Contribution of Elements)
Mean IOP following treatment with travoprost 0.004%/timolol 0.5% was statistically significantly lower than mean IOP following treatment with timolol 0.5% at all nine visits and times throughout the study in both the intent-to-treat ($p=0.009$) and per protocol ($p=0.016$) analyses. Mean IOP differences ranged from 1.5 and 2.7 mm Hg. Results of the PP analyses were consistent with those of the ITT analysis. IOP changes from baseline differences were in favour of travoprost 0.004%/timolol 0.5% over timolol 0.5%, and ranged from 1.9 to 3.3 mm Hg. Therefore, superiority of travoprost/timolol over timolol BID can be concluded.

Travoprost/timolol Eye Drops produced greater IOP-lowering than Travatan at all times. However, statistically significant differences over Travatan were only achieved in five out of the 9 time points throughout the study duration. In fact, at the 3-month and at 6-month visits, statistically significant differences over Travatan were only seen at 8AM time-point, which is surprising considering that the comparison is between the travoprost/timolol trough with the Travatan peak effect. Mean IOP differences between treatment groups ranged from 0.4 to 1.8 mmHg. Mean IOP changes from baseline show differences in favour of travoprost 0.004%/timolol 0.5% over Travatan, and ranged from 1.0 to 2.4 mmHg and from 0.7 to 2.3 mmHg, respectively, in the ITT and PP analyses, respectively, and were statistically significant at seven of nine visits and times in both analyses ($p<0.05$). The superiority of travoprost/timolol over Travatan for the mean IOP and for the IOP changes from baseline has been demonstrated for the majority, although not all, time points. However, results of the responder analysis confirm the superiority of the fixed dose combination with responder rates at 3-month of 39%, 44.4% and 48.8% in the travoprost/timolol group, 20.2%, 26.2% and 32.1% in the travoprost group and 20%, 26.4% and 30.8% in the timolol group, at 8AM, 10AM and 4PM, respectively.

Mean IOP for Travoprost/Timolol Eye Drops, TRAVATAN and Timolol 5 mg/ml Eye Drops (C-01-69 Intent-to-Treat Data)



TRAV/TIM = Travoprost 40 µg/ml / Timolol 5 mg/ml Eye Drops, Solution

The superiority of the fixed dose combination travoprost/timolol over Travatan and timolol in monotherapy can be concluded.

Study C-01-70 and Study C-02-41 (Safety/Efficacy Studies)
In Study **C-01-70**, Travatan plus timolol produced greater IOP reduction at all time-points. Treatment-group differences in mean IOP between the fixed and free combination products ranged from 0.1 to 1.1 mmHg in favour of the concomitant therapy.

The non-inferiority of travoprost/timolol eye drops over Travatan plus timolol was seen in 6 out of 9 time points, while in 3 out of 9, the upper confident limit for the differences in mean IOP between treatment groups were not within 1.5 mmHg. Only at 8AM time point, the non-inferiority was shown at all study visits. Although the non-inferiority of travoprost/timolol over Travatan plus timolol has not been consistently demonstrated at all time points, differences between treatment groups were close to the non-inferiority limit (below the 1.7mmHg) in all cases, which suggest that there are no major differences between treatment groups.

Results of Study C-02-41 were consistent to that seen in Study C-01-70, with Travatan plus timolol producing greater IOP reductions. Treatment group differences ranged from 0.3 to 1.1 mmHg in the PP analysis. Differences were out of the upper confidence interval (CI) limit of non-inferiority in 3 out of 9 time-points favouring the co-administration of Travatan plus timolol. Results of this study are consistent to those seen in Study C-01-70. The non-inferiority of travoprost/timolol Eye Drops over the concomitant administration of timolol plus Travatan was not shown at all time points. However, differences were close to the established limit of non-inferiority between treatment groups (below 1.8 in all cases), supporting the lack of major differences.

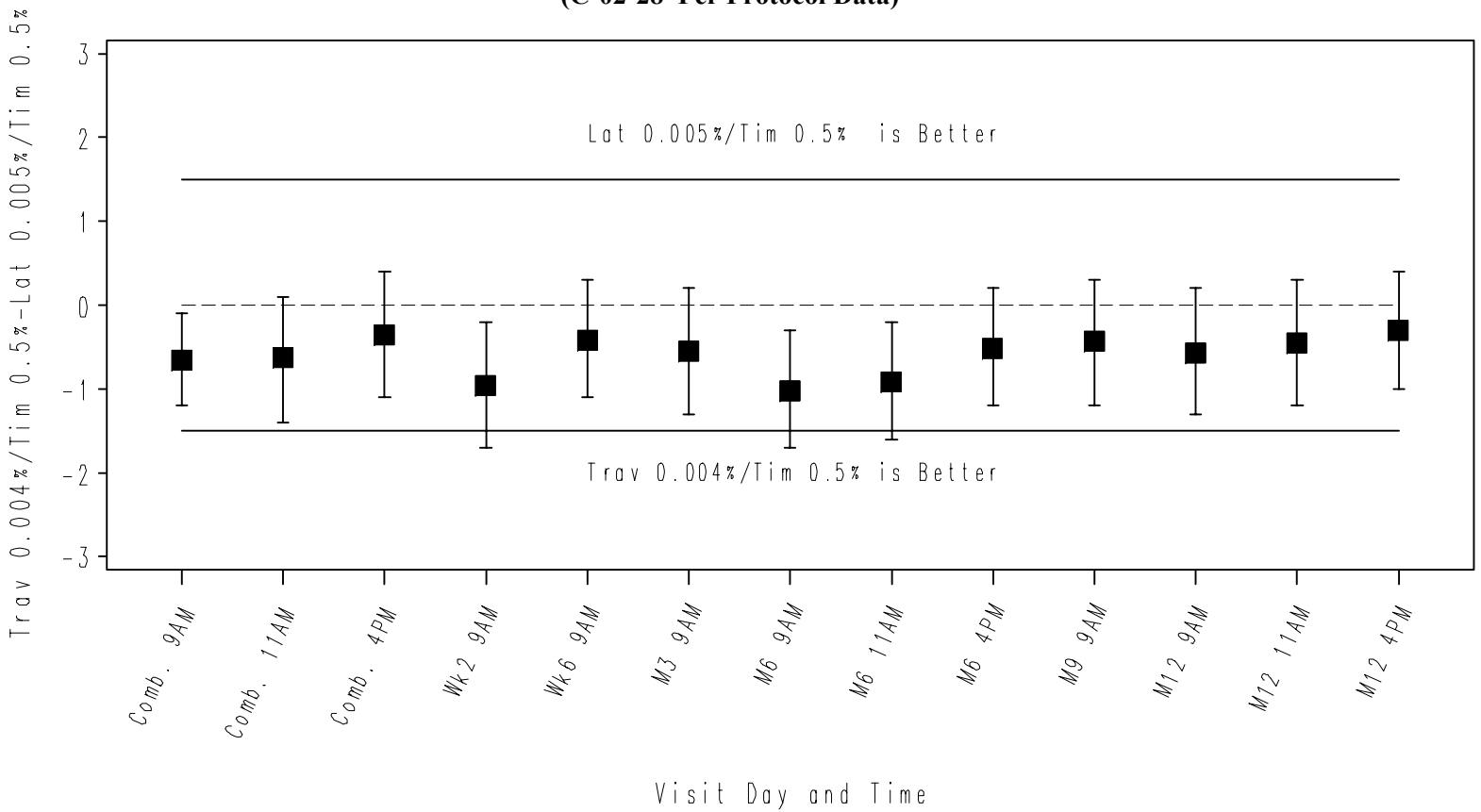
The superiority over timolol 5mg/ml twice daily can be concluded, with lower 95% CI limit out of –1.8 in all study visits and IOP measures. Mean IOP differences in favour of travoprost/timolol range from 0.9 to 2.1mmHg in the ITT analysis.

Study C-02-28 (Safety/Efficacy Study – Comparative)
Mean baseline IOP in the per protocol data set ranged across the day from 24.6 to 27.0 mmHg for the travoprost/timolol Eye Drops group and from 25.2 to 27.3 mmHg for the Latanoprost/timolol Eye Drops group.

The results of C-02-28 demonstrate that travoprost/timolol Eye Drops produces IOP-lowering that is non-inferior to Latanoprost/timolol Eye Drops. The upper 95% confidence limit for mean IOP was less than +1.5 mmHg at all study visits and times.

The per protocol results were confirmed in the intent-to-treat analysis, in which all upper 95% confidence limits were also less than +1.5 mmHg. Travoprost/timolol Eye Drops produced statistically significant and clinically relevant reductions from baseline in IOP, with mean reductions ranging from approximately 8 to 10 mmHg. Further, up to 62% of patients achieved IOP levels <18 mmHg at one or more time-points at all visits. Therefore, the non-inferiority of the fixed dose combination of travoprost/timolol Eye Drops over the currently approved fixed dose combination of Latanoprost/timolol has been convincingly demonstrated.

IOP Least Squares Means Differences (mmHg) Between Travoprost/Timolol Eye Drops and Latanoprost/Timolol Eye Drops and 95% Confidence Intervals (C-02-28 Per Protocol Data)



Trav 0.004%/Tim 0.5% = Travoprost 40µg/ml/Timolol 5 mg/ml Eye Drops, Solution
Lat 0.005%/Tim 0.5% = Latanoprost 50µg/ml/Timolol 5 mg/ml Eye Drops, Solution
Comb. = Results pooled across Week 2, Week 6, and Months 3, 6, 9 and 12.

Ancillary analyses
No ancillary analyses have been performed.

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

Difference in Mean IOP Between Treatment Groups and 95% Confidence Intervals (Per Protocol Data Sets)

Visit and IOP Measurement Time		C-01-70		C-02-41		Pooled Across Studies (C-01-70 and C-02-41)	
		Trav/Tim – TRAV + Tim		Trav/Tim – TRAV + Tim		Trav/Tim – TRAV + Tim	
		Δ	95%CI	Δ	95%CI	Δ	95%CI
Week 2	8 AM	0.1	-0.5, 0.8	0.6	-0.1, 1.3	0.4	-0.1, 0.9
	10 AM	0.3	-0.4, 0.9	1.1*	0.4, 1.8	0.7*	0.2, 1.2
	4 PM	0.5	-0.2, 1.1	0.8*	0.0, 1.5	0.6*	0.1, 1.1
Week 6	8 AM	0.1	-0.5, 0.8	0.3	-0.4, 1.1	0.2	-0.3, 0.7
	10 AM	1.0*	0.4, 1.7	1.0*	0.3, 1.7	1.0*	0.5, 1.5
	4 PM	0.9*	0.3, 1.6	0.7*	0.0, 1.5	0.8*	0.4, 1.3
Month 3	8 AM	0.6	-0.1, 1.2	0.4	-0.3, 1.2	0.5*	0.0, 1.0
	10 AM	1.0*	0.4, 1.6	0.7	-0.1, 1.4	0.8*	0.3, 1.3
	4 PM	0.9*	0.2, 1.5	0.9*	0.1, 1.6	0.9*	0.4, 1.4
Month 6	8 AM	0.6	-0.0, 1.3	0.6	-0.2, 1.3	0.6*	0.1, 1.1
	10 AM	0.9*	0.3, 1.6	1.3*	0.6, 2.1	1.1*	0.6, 1.6
	4 PM	0.5	-0.1, 1.2	0.8*	0.1, 1.6	0.7*	0.2, 1.2
Pooled across visits	8 AM	0.4	-0.1, 0.9	0.5	-0.1, 1.1	0.4*	0.0, 0.8
	10 AM	0.8*	0.3, 1.3	1.0*	0.4, 1.6	0.9*	0.5, 1.3
	4 PM	0.7*	0.2, 1.2	0.8*	0.2, 1.4	0.7*	0.4, 1.1

Δ = Difference in mean IOP (Trav/Tim minus TRAV+Tim)
*** = Statistically significant (p<0.05)**

Studies C-01-70 and C-01-41 were pooled to assess the comparative IOP effect of travoprost/timolol as compared to Travatan plus timolol, given separately. Although individual studies were not able to demonstrate the non-inferiority effect of these two combination therapies at all time points, the analysis of pooled data across these two studies convincingly demonstrates the non-inferiority of the fixed dose combination over Travatan plus timolol coadministered, which confirm previous conclusions. The results of the pooled analysis were within the upper confidence limits of 1.5 mm Hg or less at all visits and times throughout the 3-month period, the pre-planned period for primary efficacy, demonstrating the non-inferiority of travoprost/timolol Eye Drops to the concomitant dosing of Travatan and timolol 5 mg/ml Eye Drops, Solution

- Clinical studies in special populations

No studies in special populations have been performed.

- Supportive studies

No supportive studies have been submitted.

- Discussion on clinical efficacy

Study C-02-03 (Safety/Efficacy Study – Posology)
The ideal timing of the administration was considered to be a matter of concern. The applicant was therefore requested to provide a well justified dosing recommendation helpful for prescribers, considering the results available. The applicant argued that results from two of the main efficacy studies of the fixed dose combination (i.e. Studies C-01-70 and C-02-41) showed some advantages in the mean IOP reduction with the concomitantly used dose combination, where travoprost was given at evenings and timolol at mornings. However, it is agreed, also by the CHMP that these differences appear not to be relevant. Therefore, the current posology (section 4.2 of the SPC) recommendation is considered to be appropriate allowing morning or evening administration depending on the patients' preferences. Further, section 5.1 of the SPC includes information reflecting these results.

Study C-01-69 (Safety/Efficacy Study – Contribution of Elements)
The superiority of the fixed dose combination over Travatan and timolol in monotherapy can be concluded.

Study C-01-70 and Study C-02-41 (Safety/Efficacy Studies)
The results of these two studies show a tendency towards a lower IOP reduction effect with the fixed dose combination as compared to timolol plus Travatan given separately. It is however recognised that these differences do not appear clinically relevant, and that they are counteracted by the advantages of a once daily single dose administration of the fixed dose combination eye drops. Therefore, it can be concluded that these two non-inferiority studies support the IOP reduction effect of travoprost/timolol Eye Drops (once daily in the morning) and the concomitant administration of timolol 5 mg/ml Eye Drops (once daily in the morning) plus Travatan (once-daily in the evening) in patients with open-angle glaucoma or ocular hypertension.

Study C-02-28 (Safety/Efficacy Study – Comparative)
This study demonstrated the non-inferiority of the fixed dose combination of travoprost/timolol Eye Drops to the currently approved fixed dose combination of Latanoprost/timolol, which has been convincingly demonstrated.

Indication
The current clinical development programme was aimed to demonstrate the similarity in terms of efficacy and safety of the fixed dose combination as compared to that of the concomitant use of timolol plus Travatan, which has been demonstrated. Patients included in the clinical development programme for the fixed dose combination, although previously treated with IOP lowering monotherapies, were not insufficiently responsive to these therapies, as this was not an inclusion criteria in the studies performed. (Only the comparative Study C-02-28 included this type of patients).

The IOP lowering benefit of the combination therapy in patients with an insufficient response to beta-blockers has only been convincingly demonstrated in those patients participating in Study C-97-73 (in which patients with insufficient response while on timolol therapy were randomised to add placebo or Travatan). This study was presented in the Marketing Authorisation Application for Travatan, and supported the indication for concomitant therapy.

The CHMP considers that the second line indication proposed for travoprost/timolol (DuoTrav) restricted to patients for whom monotherapy such as beta-blockers and prostaglandin analogues provide insufficient IOP reduction, is justified.

The applicant was requested to comment on how prescribers would proceed with those patients with borderline IOP control while on fixed dose combination therapy, i.e. whether to change to the concomitantly used dose combination or to change the timing of administration of the fixed dose combination (i.e. at evening). The applicant argued that it is reasonable to believe that the long-term advantage of once-daily dosing in terms of compliance greatly outweigh the ~~minimal~~ benefits of the concomitantly used combination on IOP reduction and therefore, it is not recommended switching from a fixed combination to the concomitantly used combination, as compliance may be impaired in the longer term and result in less than adequate management of patients' glaucoma. The CHMP considered the applicant's response to be acceptable.

Furthermore the applicant does however emphasize that in a non-trial setting, compliance is known to be an issue when two different bottles are used concomitantly. The applicant claims that it has been shown in clinical practice, that switching from a concomitantly used combination to a fixed combination provided additional IOP reduction owing to improved compliance. Therefore, it is reasonable to believe that the long-term benefits of once-daily dosing in terms of compliance greatly outweigh the minimal advantage of the concomitantly used combination on IOP reduction.

Recommended doses for fixed dose combination
Zimmerman and Kaufman originally demonstrated that a single dose of timolol 5 mg/ml lowers IOP for at least 24 hours. Three additional studies confirmed the 24-hour duration of action of timolol 5 mg/ml, and demonstrated similar efficacy between once-daily and twice-daily dosing. Therefore the applicant argues that, dosing the travoprost/timolol fixed combination twice-daily is unlikely to provide a larger clinical effect from the timolol component.

In conclusion, better IOP-lowering efficacy is observed with once-daily dosing of a prostaglandin analogue, and little or no long-term clinical benefit is expected from twice- daily dosing of timolol. This justifies the selection of a once-daily dosing frequency for the fixed combination travoprost/timolol Eye Drops, Solution.

Timing of administration
Results from two of the main efficacy studies of the fixed dose combination (i.e. Studies C-01-70 and C-02-41) showed some advantages in the mean IOP reduction with the concomitantly used dose combination, where travoprost was given at evenings and timolol at mornings. However it is agreed that there are no relevant differences between the morning and evening administration and the current posology recommendation is considered appropriate (i.e once daily, in the morning or evening administered at the same time each day).

The impact of the corneal thickness on the results of measurement of the IOP
The clinical trials conducted during the development of the travoprost/timolol fixed combination did not include collection of data on central corneal thickness. Corneal thickness data were collected during the clinical development of Travatan (Study C-97-71) and the results demonstrated that central corneal thickness does not significantly influence the magnitude of the IOP response to either Travatan or timolol. The lack of exploration of the central corneal thickness impact on IOP measure in the fixed dose combination studies due to the previously demonstrated absence of a relevant effect of this parameter, corneal thickness on the IOP measure for each component given separately has been reasonably justified by the applicant.

Clinical safety
- Patient exposure

The clinical development of travoprost/timolol Eye Drops consisted of 6 studies (including the the crossover pharmacokinetic study C-02-35) and included a total of 1496 participants. Of these, 15 were healthy volunteers and 1481 were patients with open-angle glaucoma or ocular hypertension.

Seven hundred twenty one patients have been exposed to travoprost 0.004%/timolol 0.5%, 200 patients to latanoprost 0.005%/timolol 0.5%, 313 patients to concomitant administration of Travatan + timolol 0.5%, 101 patients to Travatan as monotherapy, and 190 patients exposed to timolol 0.5% as monotherapy.

Of the 721 patients with exposure to travoprost 0.004%/timolol 0.5%, 15 subjects participated in the crossover pharmacokinetic study (C-02-35) during which they received 3 days of exposure to each treatment. For those patients participating in protocol C-02-03, all 92 patients had exposure to travoprost 0.004%/timolol 0.5%, with 48 having exposure once-daily in the morning and 44 having exposure once-daily in the evening during which they received up to 6 weeks of exposure. The remaining 614 patients participating in protocols C-01-69, C-01-70, C-02-28, and C-02-41 had exposure to travoprost 0.004%/timolol 0.5% in the morning during which they received up to 6 months of exposure (protocols C-01-69, C-01-70, and C-02-41: 407 patients) or up to 12 months exposure (protocol C-02-28: 207 patients).

- Adverse events (AEs)

The overall incidence of AEs in travoprost/timolol treatment group across individual studies ranged from 49.1% to 69.6% and did not significantly differ to that seen in the comparator groups, i.e. Travatan plus timolol treatment group (from 48.4 to 68.4%), latanoprost/timolol (45.5%), Travatan (52.3%) and timolol (from 48.8 to 53.3%).

Ocular hyperemia was most commonly reported in patients treated with travoprost/timolol (14.4%), Travatan plus timolol (20.8%) and Travatan in monotherapy (11.6%) as compared to those treated with timolol (1.7%) and latanoprost/timolol (4%). Patients treated with the fixed dose combination tended to report a lower incidence of hyperemia as compared to those patients with concomitant treatment with Travatan plus timolol. These differences are not considered relevant, mainly because hyperemia did not lead to a high incidence of treatment discontinuation (1.9%).

Overall Frequency and Incidence of Adverse Events Occurring at Rates Greater Than or Equal to 1.0% in Open-Angle Glaucoma or Ocular Hypertension Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41)

	Trav 0.004% /Tim 0.5%		Lat 0.005% /Tim 0.5%		TRAV + Tim 0.5%		TRAVATAN		Timolol 0.5%	
	N = 706		N = 200		N = 313		N = 86		N = 176	
	N	%	N	%	N	%	N	%	N	%
OCULAR										
Hyperemia Eye	102	14.4	8	4.0	65	20.8	10	11.6	3	1.7
Discomfort Eye	46	6.5	7	3.5	31	9.9	2	2.3	10	5.7
Pruritus Eye	34	4.8	5	2.5	17	5.4	3	3.5	4	2.3
Dry Eye	25	3.5	4	2.0	12	3.8	2	2.3	3	1.7
Visual Acuity Dec	21	3.0	4	2.0	12	3.8	5	5.8	9	5.1
Foreign Body Sensat	20	2.8	7	3.5	13	4.2	3	3.5	3	1.7
Vision Blurred	14	2.0	3	1.5	4	1.3	1	1.2	5	2.8
Cataract	12	1.7	15	7.5	2	0.6			1	0.6
Keratitis	12	1.7	1	0.5	8	2.6	1	1.2	2	1.1
Pain Eye	12	1.7	1	0.5	7	2.2	3	3.5		
Photophobia	12	1.7			6	1.9	2	2.3	1	0.6
Conjunctivitis	11	1.6	4	2.0	6	1.9	2	2.3	2	1.1
Hair Dis	11	1.6			8	2.6	1	1.2		
Staining Corneal	7	1.0			7	2.2	3	3.5	1	0.6
Allerg React	6	0.8	2	1.0	2	0.6				
Cells	5	0.7			4	1.3			2	1.1
Lid Dis	5	0.7			3	1.0	2	2.3		
Visual Field Defect	5	0.7	9	4.5	2	0.6				
Vitreous Dis	5	0.7	2	1.0			2	2.3		
Hem Subconjunct	4	0.6	2	1.0	4	1.3			1	0.6
Vision Abnorm	4	0.6	2	1.0	2	0.6			2	1.1
Blepharitis	3	0.4	3	1.5	2	0.6			1	0.6
Edema Eye	3	0.4	1	0.5	1	0.3	1	1.2	1	0.6
Optic Nerve Dis	3	0.4	2	1.0	1	0.3			1	0.6
Tearing	3	0.4			4	1.3			2	1.1
Eye Dis	2	0.3			2	0.6			2	1.1
Vision Dec	2	0.3	1	0.5	2	0.6			2	1.1
Hem Conjunct	1	0.1					1	1.2		
Macular Degenerat	1	0.1	1	0.5			1	1.2		
Corneal Abrasion			1	0.5			1	1.2	2	1.1

The above table contains related and not-related events combined.
Data for the different safety populations (i.e. overall study population, open-angle glaucoma/ocular hypertension studies population and PK study population) classified as ocular and non-ocular have been presented.

Considering the open-angle glaucoma/ocular hypertension studies population (1481 out of 1496 patients and thus the most representative), ocular hyperemia, discomfort in the eye and pruritus eye were the most common ocular AEs reported with incidences of 14.4%, 6.5% and 4.8% in travoprost/timolol, 20.8%, 9.9% and 5.4% in Travatan plus timolol, 11.6%, 2.3% and 3.5% in Travatan, 1.7%, 5.7% and 2.3% in timolol and, 4%, 3.6% and 2.5% in Latanoprost/timolol treatment groups, respectively. The incidence of ocular AEs in the travoprost/timolol treatment group were slightly lower to that seen in patients treated with Travatan plus timolol concomitantly, which suggest a better tolerance of the fixed dose combination. By contrast, Latanoprost/timolol showed a lower incidence of these common ocular AEs as compared to travoprost/timolol, however these differences do not seem to be of clinical relevance since no difference in the rate of discontinuation due to AEs were observed.

The most commonly reported ocular AEs (hyperemia, ocular discomfort and eye pruritus) were considered related to the study drug and were generally well tolerated and did not lead to a higher incidence of treatment discontinuation with the exception of hyperemia (1.9% in travoprost/timolol vs 0.0% in Latanoprost/timolol). Other treatment-related AEs that occurred with exposure to travoprost/timolol included hair disorder (changes in eyelash), blurred vision, ocular pain, photophobia and keratitis.

Regarding the non-ocular AEs in the open-angle glaucoma/ocular hypertension population, timolol in monotherapy showed slightly higher incidence of some systemic adverse events such as cardiovascular and cold syndrome, but no unexpected or abnormal rates of any AEs were seen in any study group. Hypertension was the most commonly reported non-ocular AE in all study groups (4.1% travoprost/timolol, 5.1% Travatan plus timolol, 2.3% Travatan, 5.7% timolol and 7% Latanoprost/timolol). These results are consistent to those seen in the overall study population. No unexpected AEs have been reported.

Overall Frequency and Incidence of Adverse Events Occurring at Rates Greater Than or Equal to 1.0% in Open-Angle Glaucoma or Ocular Hypertension Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41)

	Trav 0.004% /Tim 0.5%		Lat 0.005% /Tim 0.5%		TRAV + Tim 0.5%		TRAVATAN		Timolol 0.5%	
	N = 706		N = 200		N = 313		N = 86		N = 176	
	N	%	N	%	N	%	N	%	N	%
NONOCULAR										
Body As A Whole										
Cold Synd	18	2.5	1	0.5	7	2.2	3	3.5	9	5.1
Infect	17	2.4	4	2.0	8	2.6	2	2.3	4	2.3
Pain	12	1.7			3	1.0				
Headache	9	1.3	1	0.5	7	2.2	2	2.3	2	1.1
Pain Back	6	0.8	1	0.5	6	1.9				
Surgical/Medical Proc	6	0.8	2	1.0			1	1.2		
Flu Synd	5	0.7	1	0.5	2	0.6	2	2.3		
Allergy	4	0.6			10	3.2	1	1.2	6	3.4
Injury Accid	3	0.4	2	1.0	1	0.3				
Abscess	1	0.1							2	1.1
Malaise	1	0.1			3	1.0				
Neopl							1	1.2		
Cardiovascular System										
Hypertens	29	4.1	14	7.0	16	5.1	2	2.3	10	5.7
Hypotens	4	0.6			1	0.3	1	1.2	1	0.6
Bradycardia	2	0.3	1	0.5					6	3.4
Coronary Art Dis	2	0.3	2	1.0						
Migraine	1	0.1			1	0.3	1	1.2	2	1.1
Syncope							1	1.2		
Vasc Dis							1	1.2		
Digestive System										
Diarrhea	3	0.4	2	1.0	1	0.3				
Gi Dis	2	0.3	2	1.0	4	1.3	1	1.2	1	0.6
Nausea	2	0.3					1	1.2	1	0.6
Abscess Periodont							1	1.2		
Dyspepsia					3	1.0				
Gastritis							1	1.2	2	1.1
Endocrine System										
Diabetes Mell	4	0.6	2	1.0	1	0.3			3	1.7
Adren Insuffic							1	1.2		

This table contains related and not-related events combined.

Overall, the incidence of treatment related non-ocular AE in the travoprost/timolol treatment groups was lower than that seen in the Travatan plus timolol and the timolol treatment groups. There was no unexpected treatment related non-ocular AEs in any study group. A comparison of the common AEs related to beta-blocking therapy showed no major differences between treatments groups containing timolol.

Tabular data on the severity of each ocular and non-ocular AE reported by treatment group show that AEs tended to be generally mild in severity, with very few severe AEs.

Overall frequency and Incidence of Patients with Adverse Events
(C-01-69, C-01-70, C-02-03. C-02-28, C-02-41)

Treatment	Travoprost 40 µg/ml /Timolol 5 mg/ml N=706	Latanoprost 50 µg/ml /Timolol 5 mg/ml N=200	TRAVATAN + Timolol 5 mg/ml N=313	TRAVATAN N=86	Timolol 5 mg/ml N=176
	N %	N %	N %	N %	N %
Ocular	281 (39.8)	67 (33.5)	136 (43.5)	32 (37.2)	48 (27.3)
Nonocular	208 (29.5)	46 (23.0)	103 (32.9)	26 (30.2)	64 (36.4)

This table inclues both related and non-related events combined

Frequency and Incidence of Adverse Events by Overall Severity
(C-01-69, C-01-70, C-02-03, C-02-28, C-02-41)

Treatment	Travoprost 40 µg/ml /Timolol 5 mg/ml N=706			Latanoprost 50 µg/ml /Timolol 5 mg/ml N=200			TRAVATAN + Timolol 5 mg/ml N=313			TRAVATAN N=86			Timolol 5 mg/ml N=176		
Severity	**Mild N (%)**	**Mod N (%)**	**Severe N (%)**	**Mild N (%)**	**Mod N (%)**	**Severe N (%)**	**Mild N (%)**	**Mod N (%)**	**Severe N (%)**	**Mild N (%)**	**Mod N (%)**	**Severe N (%)**	**Mild N (%)**	**Mod N (%)**	**Severe N (%)**
Ocular	**226 (32.0)**	**47 (6.7)**	**8 (1.1)**	**41 (20.5)**	**23 (11.5)**	**3 (1.5)**	**119 (38.0)**	**16 (5.1)**	**1 (0.3)**	**28 (32.6)**	**4 (4.7)**	**-**	**42 (23.9)**	**6 (3.4)**	**-**
Nonocular	**91 (12.9)**	**93 (13.2)**	**24 (3.4)**	**20 (10.0)**	**20 (10.0)**	**6 (3.0)**	**53 (16.9)**	**40 (12.8)**	**10 (3.2)**	**16 (18.6)**	**9 (10.5)**	**1 (1.2)**	**37 (21.0)**	**22 (12.5)**	**5 (2.8)**

Mod – Moderate
This table includes both related and non-related events combined

No safety concerns were identified based upon an analysis of changes from baseline in ophthalmic parameters (visual acuity, cornea, iris/anterior chamber, lens, aqueous flare, and inflammatory cells, fundus parameters, cup/disc ratio, visual field and iris, eyelash, and eyelid photography.

An analysis of changes in cardiovascular parameters (pulse rate, systolic blood pressure and diastolic blood pressure) has been performed, the results of which are reassuring with no new or unexpected safety concerns. Five clinically relevant, treatment-related changes from baseline in cardiovascular parameters (1 occurrence of bradycardia, 1 occurrence of hypotension, and 3 occurrences of hypertension) were identified in patients with exposure to travoprost 0.004%/timolol 0.5%. All occurrences were mild in intensity, resolved without or were continuing with or without treatment, and did not interrupt continuing participation in the study with 1 exception (due to an occurrence of hypertension).

- Serious adverse event/deaths/other significant events

There were three deaths during the clinical studies of travoprost/timolol; all of them considered not to be related to therapy with study drug (i.e. peritonitis and cholecystitic, myocardial infarction and allergic reaction to anesthesia).

Fifty two patients (3.5%) experienced other non-fatal serious AEs. Of these, 22 (1.5%) patients were in the travoprost/timolol treatment group, 13 (0.9%) in the Latanoprost/timolol treatment group, 12 (0.8%) in patients treated with Travatan plus timolol, 2 (0.13%) in patients treated with Travatan and 3 (0.2%) in the group of patients treated with timolol. Five out of the 52 patients resulted in treatment discontinuation from study participation and none of them occurred in the travoprost/timolol treatment group

- Laboratory findings

No laboratory parameters were evaluated in the clinical trials involving travoprost/timolol Eye Drops.

- Safety in special populations

No safety concerns were identified based upon a review of ocular and nonocular adverse events by intrinsic factors, which included age, gender, race, iris colour, and the time of onset of the adverse event.

- Safety related to drug-drug interactions and other interactions

No safety concerns were identified based upon a review of ocular and nonocular adverse events by intrinsic factors, which included concomitant diseases and concomitant medications.

- Discontinuation due to adverse events

In total, 130 patients across all treatment groups discontinued patient participation in the Open-Angle Glaucoma or Ocular Hypertension studies (C-01-69, C-01-70, C-02-03, C-02-28, and C-02-41), which included 64 patients with exposure to travoprost 40 µg/ml / timolol 5 mg/ml.

Frequency and Incidence of Study Discontinuation – Open-Angle Glaucoma or Ocular Hypertension Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41)

Treatment	Overall	Lack of IOP Control	Adverse Events	Patient Decision	Lost to Follow Up	Other
Overall (N=1481)	130 (8.8%)	11 (0.7%)	72 (4.9%)	21 (1.4%)	8 (0.5%)	18 (1.2%)
Travoprost 40 µg/ml /Timolol 5 mg/ml (N=706)	64 (9.1%)	3 (0.4%)	40 (5.7%)	7 (1.0%)	6 (0.8%)	8 (1.1%)
Latanoprost 50 µg/ml /Timolol 5 mg/ml (N=200)	18 (9.0%)	3 (1.5%)	10 (5.0%)	4 (2.0%)	0 (0%)	1 (0.5%)
TRAVATAN + Timolol 5 mg/ml (N=313)	27 (8.6%)	0 (0%)	18 (5.8%)	4 (1.3%)	0 (0%)	5 (1.6%)
TRAVATAN (N=86)	11 (12.8%)	1 (1.2%)	2 (2.3%)	3 (3.5%)	2 (2.3%)	3 (3.5%)
Timolol 5 mg/ml (N=176)	10 (5.7%)	4 (2.3%)	2 (1.1%)	3 (1.7%)	0 (0%)	1 (0.6%)

The data provided do not suggest any unexpected finding based upon a review of the reasons for discontinuation across treatment groups.

- Post marketing experience

A review of the postmarketing experience with each individual component of the fixed dose combination of travoprost/timolol has been performed. The data provided confirm that Travatan and timolol are safe in the treatment of open-angle glaucoma and ocular hypertension.

- Discussion on clinical safety

Travoprost/timolol Eye Drops administered once-daily is safe and well-tolerated in patients with open-angle glaucoma or ocular hypertension based upon an overall review of adverse events which includes an assessment of seriousness (serious/non-serious), treatment relatedness, most common events and rate of discontinuation due to adverse events.

A similar safety profile was observed comparing therapy with the combination product (travoprost/timolol Eye Drops) to concomitant therapy with the individual components (Travatan + timolol 5 mg/ml) or monotherapy with each component (Travatan; timolol 5 mg/ml).

No clinically relevant differences were observed when comparing the safety profiles of travoprost/timolol Eye Drops and latanoprost/timolol Eye Drops in patients with open angle glaucoma or ocular hypertension having up to 12 months of exposure to study drug.

Overall travoprost/timolol Eye Drops administered once-daily is safe and well-tolerated in patients with open-angle glaucoma or ocular hypertension based the assessment of adverse events.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

An extensive description of the pharmacovigilance system was provided. The applicant argued that there is an extensive pharmacovigilance plan for Travatan, mainly focusing on those specific AEs of prostaglandin analogues such as iris pigmentation, and thus, it was considered that new studies for DuoTrav were not deemed necessary. However, the implications of any relevant safety information that could change the safety profile of Travatan should also be discussed for DuoTrav.

Risk Management Plan

The applicant submitted a risk management plan.

Travatan has been authorized in similar ophthalmic formulation for over 4 years and timolol in an ophthalmic formulation for more than 20 years on a global basis.

The Risk Management Plan did not identify any specific safety issues relating to the use of the combined product compared to the use of the individual components.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this 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 have been investigated and are controlled in a satisfactory way

Non-clinical pharmacology and toxicology

The pharmacology of both agents travoprost and timolol are well known. Consequently no new non-clinical ocular or systemic pharmacology studies were conducted on the travoprost/timolol fixed combination. The non-clinical pharmacology conducted on travoprost to support the Marketing Authorisation for Travatan and selected reviews of the timolol scientific and medical literature have been presented to support the current Marketing Authorisation Application.

Comparison of the data from individual and concomitant administration of travoprost and timolol showed similar pharmacokinetics for both analytes, demonstrating no pharmacokinetic interactions for travoprost and timolol administered concomitantly by the topical ocular route.

The pharmaco-toxicological profiles of the individual active substances, travoprost and timolol, have been extensively investigated. On the basis of the available results provided by the applicant, it can be concluded that DuoTrav (travoprost/timolol) is well tolerated.

Efficacy

The claimed indication is restricted to patients for whom other therapies provide insufficient IOP reduction, which is considered to be justified by the current clinical practice that recommends starting with monotherapy at maximum doses and to switch to combined therapy as a second step in those patients with insufficient control with monotherapy.

Patients included in the clinical development programme for the fixed dose combination, although were previously treated with different IOP lowering agents, were not insufficiently responsive or intolerant to these therapies.

The restriction of the indication to patients with insufficient response to monotherapy such as beta-blockers or prostaglandin analogues, is based on the fact that the IOP lowering benefit of the combination therapy has only been convincingly demonstrated in Study C-97-73 (submitted in the Marketing Authorisation Application for Travatan), in which patients with insufficient response while on timolol therapy were randomised to add placebo or Travatan.

Therefore, the wording agreed by the CHMP is: “Decrease of intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (see Section 5.1)”.

Safety

From the safety database all the adverse reactions reported in clinical trials have been reviewed and are summarised in the Clinical safety section.

- User consultation

A user testing with adults respondents in the age range for which Avantra (the previously proposed trade name for DuoTrav) might be prescribed was performed by the applicant. The main interview took place in September 2005. Ten full interviews were carried out. There was a pilot interview and some amendments to the leaflet that were agreed by the applicant. The results showed that the current user leaflet was successful. However, the applicant considers that some minor areas could be improved such as to: clarify the pictures, make actionable advice about side effects more prominent and modify the bolding within the ‘Take Special Care’ section. Further modifications of the name of the medicinal product were suggested by the applicant, which were considered to be acceptable.

Risk-benefit assessment

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.

The existence of a fixed dose combination of travoprost and timolol is considered justified according to the Note for Guidance on Fixed Combination Medicinal Products (CPMP/EWP/240/95) based on the simplification of therapy. Compliance with treatment, which is a known factor of possible improvement in IOP control, further supports this fixed-dose combination.

The benefit of the concomitant administration of Travatan plus timolol was demonstrated at the time of the granting the marketing authorisation for Travatan. The fixed dose combination of travoprost/timolol Eye Drops has now demonstrated to produce some greater mean IOP reductions than those produced by either Travatan or timolol alone. More relevant is the non-inferiority of the fixed dose combination compared to the concomitantly used dose combination of Travatan plus timolol, which has been convincingly demonstrated, as well as the non-inferiority with the currently marketed fixed dose combination of a prostaglandin analogue latanoprost and timolol. Therefore, the efficacy as well as the safety and tolerance of the fixed dose combination of travoprost/timolol eye drops solution known as DuoTrav is considered to be adequately demonstrated.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of DuoTrav in the treatment of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension was favourable and therefore recommended the granting of the marketing authorisation.