SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Lumigan. This scientific discussion has been updated until 1 June 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$. It is currently indicated for the reduction of elevated IOP in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers). The product is presented as a 0.3 mg/ml eye drops solution.

Glaucoma is the leading cause of irreversible blindness in the world. It is a frequent disease and it has been estimated that 66.8 million have glaucoma, 6.7 million of who are bilaterally blind. Open angle glaucoma is the most common type, mainly primary but also, in some cases open angle glaucoma is secondary to the exfoliation syndrome or other primary ocular diseases.

Open angle glaucoma is characterised by an optic neuropathy that leads to loss of optic-nerve tissue with an excavation of the ophthalmoscopically visible optic nerve head and consequently, to a progressive loss of vision. The aetiology is multifactorial. Elevated IOP is the main risk factor for its development and reduction of IOP has been demonstrated to protect against further damage to the optic nerve, even in patients with IOP that is statistically "normal" (so called normal tension glaucoma). Other risk factors for the development of open-angle glaucoma include inheritance, age, race, myopia and cardiovascular disease.

Up to 10% of people over the age of 40 years have IOP above 21 mmHg (normal range 10 to 21 mmHg). Those who have IOP above 21 mmHg (but below 30 mmHg) but no optic nerve damage and no risk factors are considered to have ocular hypertension. Patients with ocular hypertension have an increased risk of progressing to real glaucoma. Recent data suggest that treatment with topical ocular hypotensive medication is effective in delaying or preventing the onset of glaucoma in such patients.

The overall purpose of treatment in open angle glaucoma is to preserve visual function without causing untoward effects from therapy. Treatment is focused on lowering IOP by pharmacological means, surgically, or with lasers. The treatment aims to maintain the IOP at a pressure below which further optic nerve damage is unlikely to occur in the single patient. The target pressure is individually chosen and should be maintained at a safe level at which the progression of damage is arrested or acceptably slow. The target IOP for each patient is initially chosen according to the current amount of optic damage and the pressure at which the damage occurred, but it will be further adjusted according to the disease progression in subsequent examinations of visual field. Although different clinical aspects will guide the choice of the target initial pressure, it is common to pursue a decrease of the IOP between 20% and 40% depending on the degree of associated damage. Once the patient has achieved a "safe" IOP at which the disease does not progress, additional lowering of the IOP would provide marginal benefit entailing a higher risk of adverse reactions.

The IOP can be lowered by medical treatment, laser surgery, and incisional surgery (alone or in combination). The choice of initial therapy depends on numerous considerations, and discussion of treatment should include all appropriate options. In most instances, pharmacological therapy constitutes the initial step, moving to laser trabeculoplasty as an alternative when medical treatment, often in combination, has failed or is unsuitable. Filtering surgery is usually done as the last step, after failing the previous approaches.

At the time of the initial approval of Lumigan treatment guidelines recommended that medical treatment starts with a topical drug, a beta-blocker if contraindications are not present. Since that time prostaglandin analogues have been approved for use as first-line therapy. If necessary, a second topical drug is added or tested in monotherapy. The possible second line drugs are alpha-adrenergic agonists (such as brimonidine or apraclonidine) or carbonic anhydrase inhibitors (such as dorzolamide or brinzolamide). Other treatments such as topical cholinergic agonists or systemic carbonic anhydrase inhibitors have a more limited value.

Beta-blockers, and particularly timolol, which is the most popular product, have an excellent pressure-lowering efficacy, long duration of action and few ocular side effects. However rare, systemic side effects of topical beta-blockers (bronchospasm and cardiac side effects) may limit its use in special populations (patients suffering from asthma, chronic obstructive pulmonary disease, bradycardia, and elderly in general).

Prostaglandin analogues are the most recent pharmacological group to treat topically open angle glaucoma. Instead of decreasing the production of aqueous humour produced by the ciliary body, as the majority of the above mentioned pharmacological treatments, these products lower the IOP by means of increasing the aqueous humour outflow through the uveoscleral pathway. Latanoprost was the first approved product within this pharmacological group followed by travoprost. Bimatoprost was then approved in Europe in March 2002. In Europe latanoprost went through mutual recognition procedure and was accepted in all Member States, with the indication of reduction of elevated intraocular pressure in patients with open angle glaucoma and ocular hypertension intolerant or with insufficient response to any other therapy. The product has good activity, duration of action that allows the administration once a day and few systemic side effects. There is still some caution with the long-term consequences derived of its new mechanism of action and some unusual ocular side effects such as the irreversible darkening of the iris or the appearance of cells and flare. Bimatoprost is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ but its IOP lowering effect is claimed not to be related to prostaglandin receptors.

In medical practice, those patients who have ocular hypertension should be periodically examined (optic nerve, visual fields) to determine whether there is evidence of progressive damage which would indicate the need to start with treatment. The decision to begin treatment to lower IOP in ocular hypertension is complex and depends on when ocular, systemic, medical, and psychosocial risk factors will show up (primary open angle glaucoma suspect). Any patient who shows deterioration of the optic nerve status (optic nerve head appearance or visual field) consistent with glaucomatous damage should be diagnosed as having primary open angle glaucoma and treatment instigated. Whilst in the past it was considered that for the majority of glaucoma suspect, treatment may not be considered necessary, recent data suggest that ocular hypotensive therapy can be effective in delaying or preventing the onset of glaucoma in such cases.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Lumigan eye drops is formulated as 0.03% aqueous, sterile, preserved, isotonic, multidose ophthalmic solution using well-known excipients. It contains bimatoprost (0.3 mg/ml) as active substance and benzalkonium chloride (BAC) (0.005%) as preservative. Excipients include sodium chloride, sodium diphosphate dibasic heptahydrate, citric acid monohydrate and purified water.

The solution (3 ml) is packaged in a 5 ml multiple dose blow-moulded LDPE bottle with a cap of polystyrene, coloured white by the addition of titanium dioxide to the resin. Container/closure integrity has been demonstrated. No deleterious interaction of the primary packaging material with bimatoprost has been observed

Active substance

Bimatoprost is a new active substance, a synthetic prostamide, structurally related to dinoprost (prostaglandin F2α). The molecule has 5 chiral centres and “cis-trans” isomerism, the “cis” isomer being the selected form.

Bimatoprost is (Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(1E, 3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentenyl]-N-ethyl-5-heptenamide. Evidence of structure has been proven by elemental analysis, IR, UV, 1H-NMR, 13C-NMR, 2D Cosy-NMR, 2D HMQC NMR and MS. X-ray crystallography on an intermediate has confirmed the absolute configuration of the four chiral centres in the cyclopentane ring.

Specifications for all starting materials, intermediates, solvents and reagents and of isolated intermediates are provided and are acceptable. All in-process testing requirements are appropriately indicated for each step of the process. The specification includes relevant tests and impurity levels in the specification are justified by toxicology studies.

3 validation batches comply with the specification. Stability data support the retest period of 6 months when stored in the proposed container at ≤-15°C.

Other ingredients

All excipients comply with PhEur monographs where relevant, except sodium phosphate dibasic heptahydrate, which complies with USP. The microbiological purity of the excipients is generally not more than 100 CFU/g except for the pH adjustment by strong acids and strong bases.

Product development and finished product

The preserved formulation used in clinical trials is identical to the composition and strength applied for. The excipients chosen are commonly used in ophthalmic products and to minimise irritation physiological pH (7.3) is chosen. Optimum pH for stability of the finished product is between pH 6 and 8. The active substance stability is good in the buffer system chosen (sodium phosphate and citric acid).

The strength 0.3 mg/ml is chosen based on dose-response studies and because the solubility of bimatoprost in this concentration is sufficient to exclude a solubilising agent. The preservative benzalkonium chloride (BAC) is used at a concentration of 0.005% and the specifications ensure that PhEur criteria A preservative efficacy is met throughout the shelf-life of the product.

No manufacturing overages are used. No reprocessing of bulk or finished product will be applied. Excipients are added to the vessel containing purified water one by one followed by the active substance. All substances are dissolved during mixing. The bulk product is sterilised by filtration through 0.2 µm sterilising cartridge filter and filled aseptically in a class A environment into bottles previously sterilised by validated process of exposure to ethylene oxide. Equipment is sterilised by moist steam autoclaving and steam-in-place where the minimum of F_0 is 21 minutes. Reproducibility of the manufacturing process has been demonstrated. The primary packaging is sterilised by use of EtO. The EtO residuals meet the acceptance criteria of <1ppm, as recommended in the current CPMP/QWP guideline.

Specifications

The specification for content of active substance at release is 95-105% of label, and a slightly broader specification, which does not compromise the efficacy and the safety of the product, has been established for the end of shelf-life.
Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.
The preservative BAC is controlled at release within the limits 90-110% of the stated amount.
Other tests include pH, osmolality, colour, visual clarity, particulate matter and sterility. All control methods have been validated in a satisfactory way.
Three validation batch analyses from the manufacturing site confirm satisfactory uniformity of the product at release.

Stability of the product

Primary registration batches and Primary stability batches: Due to temperature dependent water loss a rise in assay bimatoprost, osmolality and preservative is seen. All results are within the proposed shelf-life specifications. No significant changes are observed at 40°C/20%RH.
No significant difference is observed for samples stored at 25°C/40%RH and 40°C/20%RH in upright or inverted position. For batches with higher fill volume the % water loss is reduced and likewise results on assay, osmolality and preservative content show lower rise in value. No rise in degradation products is observed at any storage condition.

All preservative efficacy data remain constant through the study periods at 25°C/40%RH, 30°C/40%RH and 40°C/20% RH. All batches were subjected to an initial preservative efficacy test and subsequent testing occurred at least annually and/or at the end of the study period.

Results have been generated by validated, stability indicating methods and indicate satisfactory stability in solution. These results support the (unopened) shelf-life stated in the SPC, i.e. 24 months when stored at "no special precautions for storage". An in-use period of 28 days maximum is normal for an ophthalmic product of this type.

3. Part III: Toxico-pharmacological aspects

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). It is made by replacement of the carboxylic acid group of $PGF_{2\alpha}$ by an electrochemically neutral substituent. As the carboxylic acid group is critical for the interaction of the molecule with $PGF_{2\alpha}$-sensitive receptors (FP receptors), bimatoprost does not show any significant pharmacological activity at these receptors. The mode of action of bimatoprost appears to be similar to that of $PGF_{2\alpha}$ 1-ethanolamide (prostamide $F2_{2\alpha}$), a naturally occurring substance that is derived from anandamide by cyclooxygenase (COX-2) in the prostamide pathway. This pathway leads to the formation of endogenous lipid amides that lower IOP.

Pharmacodynamics

- *In vitro* studies

The pharmacology of bimatoprost has been studied by receptor binding assays, using functional and radioligand binding methods. These studies show that bimatoprost exhibits a pharmacological activity profile different from that of $PGF_{2\alpha}$ and other classical prostanoid FP receptor agonists in that bimatoprost does not produce typical FP receptor mediated effects, such as contraction of the human uterus and cell proliferation. Bimatoprost also shows no activity at other known prostanoid receptors.

- *In vivo* ocular pharmacology studies

Topically administered bimatoprost reduced the IOP in ocular normotensive dogs and monkeys. In ocular hypertensive monkeys, bimatoprost was highly effective in reducing IOP as a single dose.

The mechanism of action of bimatoprost was studied in dogs and monkeys. In monkeys, the fluorphotometry showed that bimatoprost did not alter aqueous humour inflow and that bimatoprost increases uveoscleral outflow by 42% without affecting total outflow facility (a parameter of conventional, trabecular outflow), and therefore bimatoprost appears to decrease IOP by stimulating uveoscleral outflow. Similarly, in dogs, bimatoprost did not affect total outflow facility. It is noted that in humans bimatoprost also increases uveoscleral outflow, but as this change does not entirely account for the IOP decrease, increased conventional outflow facility might act as an additional mechanism.

- Pharmacodynamic drug interactions

To study compatibility of bimatoprost with timolol in ocular formulations, an assessment of ocular discomfort following topical applications to rabbits of isotonic and hypotonic formulations of 0.03% bimatoprost-0.5% timolol was made. The isotonic formulation was found to be well tolerated. When applying these formulations to the eyes of dogs, both iso- and hypotonic formulations were well tolerated. It was concluded that adverse effects of using bimatoprost and timolol as adjunctive therapy were not anticipated.

- General and safety pharmacology programme

Ocular blood flow

The vasomotor activity of bimatoprost was examined, using human retinal tissue grafted into the hamster cheek pouch membrane. Bimatoprost did not significantly affect retinal arteriolar diameter.

In ocular safety studies on rabbits and dogs, bimatoprost and placebo produced transient slight ocular discomfort and conjunctival hyperaemia.

Pupil diameter

In cats and dogs, iris is constricted by bimatoprost, as shown by *in vitro* and *in vivo* studies. The miosis is considered to be species-specific, as monkeys and humans did not show this effect.

Iridial hyperpigmentation

A study in cynomolgus monkeys showed that bimatoprost 0.1% given twice daily for one year lead to iris darkening. The iris darkening was accompanied by increased melanogenesis. It was interpreted that melanosome maturation leads to iridial hyperpigmentation. With a lower dose of 0.01%, there were no iris colour changes. One year of topical treatment with Latanoprost (0.005%) or bimatoprost (0.03%) in cynomolgus monkeys lead to pronounced iris darkening in the Latanoprost-treated animals. Slight iris darkening was observed for all other treatment groups including controls, and was presumed to be related to ageing.

Uterotonic activity

As opposed to $PGF_{2\alpha}$ and other FP receptor agonists, bimatoprost did not show uterotonic activity in either pregnant or non-pregnant human uterus preparations. There was also no uterotonic activity of bimatoprost in rat and mouse isolated uterus, but in rabbit isolated uterus, bimatoprost had potent contractile activity.

Activity at human TP receptors

A study was conducted to determine the effect of bimatoprost on contraction of the human isolated umbilical artery. The EC_{50} value for bimatoprost was >10000 nM at the 10 µM concentration. The effects of bimatoprost were significantly lower than the effects of $PGF_{2\alpha}$ at the 10 µM concentration. It was concluded that bimatoprost has minimal potential for evoking TP receptor mediated events. TP receptors are associated with uterine, cardiovascular and airway smooth muscle.

Cardiovascular effects

Cardiovascular effects of bimatoprost were compared to those of $PGF_{2\alpha}$. *In vitro,* bimatoprost had only very weak relaxing effect (EC50>2000 nM) on precontracted, endothelium intact rabbit jugular vein. *In vivo,* there was a small, transient arterial blood pressure increase (10-12%) and an 8% decreased in heart rate in anaesthetised rats given i.v. bimatoprost. At low i.v. doses, bimatoprost had no effects on blood pressure, heart rate, electrocardiogram, or respiration rate of conscious dogs. At 10 µg/kg i.v. there was a transient mean blood pressure increase.

Gastrointestinal and renal effects

At low doses, bimatoprost had only very low activity in isolated mouse, guinea pig, chick, rat and gerbil digestive tract tissue. However, at 1 mg/kg, bimatoprost significantly inhibited the small intestinal charcoal transit by 24.5%. Similarly, only the high (1 mg/kg) dose of bimatoprost significantly increased urine volume and urinary excretion of electrolytes (Na^+ and Ca^{++}) while lower doses were devoid of effects.

Pharmacokinetics

Ocular absorption

Ocular absorption studies were conducted in rabbits and monkeys. In monkeys, significant concentrations of intact bimatoprost were detected in the iris and the ciliary body. AUC values for the iris and ciliary body were 19-56 times higher than those of the aqueous humour. Twenty-four hours after ocular administration, bimatoprost concentrations in the ciliary body and muscle were still more than 5-fold higher than the *in vitro* EC_{50} value required for pharmacological effect (found in the cat ciliary body and muscle). In another study in monkeys, significant concentrations were produced in the iris and ciliary body while systemic concentrations of radioactivity were very low after multiple

ophthalmic doses of tritiated bimatoprost. In rabbits, after a single topical administration of tritiated bimatoprost, significant concentrations were produced in the uvea (iris and ciliary body) while systemic blood and plasma concentrations were very low.

Systemic absorption

Ocular instillation of ^{3}H-bimatoprost to rabbits and monkeys resulted in plasma C_{max} of total radioactivity that were one to three orders of magnitude lower than the ocular tissue concentrations. In fasting animals given 4 mg/kg of 0.2% bimatoprost orally, systemic bioavailability of bimatoprost was 40% in mice, 29% in rats and 3% in monkeys.

Distribution

The steady-state volumes of distribution after IV administration to mouse, rat, monkey and man were 2.4, 6.0, 2.2 and 0.67 l/kg, respectively. In mouse, rat, rabbit and monkey plasma, between 63 and 72% of bimatoprost was bound to plasma protein. After a single intravenous dose of tritiated bimatoprost, highest levels of drug-related material occurred in the main excretory organs (gastrointestinal tract, liver, kidney and urinary bladder), suggesting that biliary excretion and/or intestinal secretion may play a role in the disposition of bimatoprost. Drug-derived material did not penetrate the blood-brain barrier or distribute extensively into the erythrocytes, adrenals, heart, pancreas, spleen or thyroid.

Ocular metabolism

In the rabbit eye, but not in the monkey or human eye, there was an extensive metabolism of ^{3}H-bimatoprost to AGN 191522, a potent impurity and Cl-acid metabolite of bimatoprost. Two to six metabolites were detected in various ocular tissues of the rabbit. In monkeys, there was minimal metabolism of bimatoprost to AGN 191522 and to three other minor metabolites.

Systemic metabolism

Metabolite profiles of bimatoprost were investigated in blood, urine and faeces following a single i.v. administration of tritiated bimatoprost to mice, rats and monkeys. Bimatoprost and AGN 191522 were both detected in the blood of all species following intravenous dosing. The major circulating drug-related component found in mouse, rat and monkey was bimatoprost, while AGN 191522 was the major component in rabbit blood. The blood, urinary and faecal metabolite profiles obtained following i.v. administration of tritiated bimatoprost to rats, monkeys and humans were comparable.

In vitro metabolism

The percentage of ^{3}H-bimatoprost that was metabolised by liver slices over 18 hours was 89% in rat liver, 84% in male monkey liver, 58% in female monkey liver, 83.2% in dog liver and 77% in female human liver. Studies using human liver microsomes and recombinant human P450 isozymes identified CYP3A4 as the enzyme responsible for the hydroxylation of bimatoprost. In a one-month study where monkeys were given 1 mg/kg bimatoprost i.v., resulting in drug exposures 4000 times greater than seen in humans after ophthalmic administration, bimatoprost had no significant effect on any of the hepatic microsomal enzyme activities (CYP1A2, CYP2A6, CYP2B1/2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, CYP4A9/11). In a similar study in rats, an increased activity of UDP-glucuronosyl transferase was observed in female rats and a marginal reduction in the rate of testosterone 16β –hydroxylation was found in male rats.

Elimination

In rabbits, the ocular tissue concentrations of intact bimatoprost declined rapidly after ophthalmic administration. The elimination half-life ranged from 0.74 to 2.3 hours. Elimination half-lives after IV administration of 1 mg/kg was 0.54 hours in mice, 0.26 hours in rats, 8.4 hours in monkeys and 0.77 hours in humans. Mean blood clearance was 12 l/h/kg in mice, 9.5 l/h/kg in rats, 2.4 l/h/kg in monkeys and 1.5 l/h/kg in humans. Urinary excretion after IV administration of ^{3}H-bimatoprost was 42% of total radioactivity in female rats and 27% in male rats, while faecal excretion was 69% in males and 49% in females. In monkeys, both males and females had a larger excretion of total

radioactivity in urine (58-64%) than in faeces (24-31%). In humans administered ^{3}H- bimatoprost IV, 67% was urinary excreted and 25% was excreted in faeces.

Toxicology

Toxicokinetics

Measurements of systemic exposure to bimatoprost have been conducted in different animal species. The C_{max} and AUC values of bimatoprost increased proportionally with the administered dose, and the steady state blood concentrations were achieved in all repeated dose-toxicology studies. There was no drug accumulation in rabbits treated ocularly for 6 months or monkeys treated ocularly for 1 year.

Single dose toxicity

After single i.p. dose of 96 mg/kg of bimatoprost to mice there were no significant findings concerning clinical observations, mortality, body weight or gross pathology. Similarly, i.v. doses of up to 3 mg/kg produced no adverse effects in mice. The dose of 3 mg/kg represents a dose 1000 times higher than systemic human exposure assuming an ocular dose of one drop BID of 0.1% ophthalmic solution is given in humans.

Repeated dose toxicity studies

In mice, toxicity of orally administered bimatoprost was assessed in studies of 2 week, 4 weeks and 13 weeks duration. In the 4-week study, the only observed possibly treatment-related change was a tendency toward haemoconcentration. In the 13-week study, medullary lymphoid proliferation in the thymus, acute inflammatory cells in the superficial layers of the vagina and increased numbers of corpora lutea were detected. The thymic changes had regressed after the recovery period, and the vaginal changes had partially regressed.

In rats, toxicity of orally administered bimatoprost was evaluated in rats in 2-week studies, 4 weeks, 13 weeks, and a 1-year study. In the two-week studies, the high dose of 16 mg/kg/day produced drug related testicular changes of bilateral degeneration of the testis and increased abnormal germ cells in the tubular lumen of the epididymis. An increase in vacuolisation of the cortical cells in the adrenal glands was also present among animals in all bimatoprost treated groups. In the 13-week study, decreased bodyweight and mildly increased serum enzymes were observed. The changes reversed after the recovery period of 4 weeks. Ovarian weight was increased in females at all dosages, and was accompanied by microscopic findings of increased numbers of prominent, vacuolated corpora lutea at all dosages. The ovarian weight increase was reversible. Statistically significantly lower epididymis weights were noted for males receiving 16 mg/kg/day. In the one year study, treatment related microscopic pathological findings were cellular vacuolation in corpora lutea of the ovaries observed at termination, with partial reversibility at 8 weeks.

The toxicity of intravenously administered bimatoprost was evaluated in studies of 1, 2 and 4 week's duration in rats. In a one-week study, there were no treatment-related deaths. Clinical signs of deceased motor activity, dyspnoea, cyanotic tail and soft stool were observed. In the high dose group, animals additionally showed signs of ataxia, gasping, ptosis, lethargy, and piloerection. Mean body weights were decreased in the 50 and 100 mg/kg dose groups and there were numerous changes in blood chemistry parameters. In the 4 week study, vacuolated corpora lutea were found in females. Toxicokinetic measurements showed that bimatoprost was rapidly eliminated from blood and the animals were exposed to steady-state concentrations throughout the study. The AUC_{de} values in the rat studies ranged from 2.5 to 4100 folds greater than the values in humans given the clinical regimen.

The ocular studies in rabbits were of 3 days, 1 month, and 6 months duration. In these studies, the main findings were transient slight conjunctival hyperaemia, transient slight ocular discomfort, but no systemic or corneal toxicity was observed. In dogs, after topical administration of bimatoprost, slight ocular discomfort, transient slight hyperaemia and miosis were observed. Miosis was noted to be an expected dog-specific pharmacological effect. The transient ocular discomfort and conjunctival hyperaemia observed in some rabbit and dog studies were believed to be connected to more frequent

dosing in these cases. Ocular sensitivity additionally appeared to be related to vehicle administration. It should be noted that similar ocular effects were not observed in monkeys.

In a 52 week study, monkeys were administered topical bimatoprost once or twice daily. Increased iridial pigmentation was observed in all drug–treated groups at week 13 and during the remainder of the study. The incidence of increased pigmentation was associated with the frequency of dosing. The increased iridial pigmentation did not reverse after treatment cessation. At week 26 to 35, periocular effects, characterised by a prominent upper and/or lower sulcus, resulting in a widening of the palbebral fissure of the treated eye, were observed in all drug-treated groups. Periocular effects completely resolved by the end of the recovery period. Since iridial pigmentation and widening of the palbebral fissure have been observed in monkeys with prostaglandin analogues, including latanoprost, these effects are likely related to this pharmacological class.

When bimatoprost was administered once daily by i.v. injection to male and female monkeys for 4 weeks, no local or systemic adverse effects were observed. In a 17-week i.v. study, similarly to the 1-year ocular study, a reversible increase in the prominence of the periocular sulci was observed in all drug-treated groups. These effects occurred after 9 weeks of treatment. No systemic effects occurred at any dose.

Reproductive toxicity

Reproductive toxicity studies were conducted in mice, rats and rabbits. However, the rabbit was precluded as a species to evaluate embryo-foetal developmental toxicity. In mice, maternal toxicity such as decreased number of pregnancies, abortions or resorptions was seen at doses of 0.3 mg/kg/day or higher. At the lowest-observed-adverse-effect-level (LOAEL) for maternal toxicity (0.3 mg/kg/day), the AUC_{de} was 33 times higher than the AUC_{de} in humans given the clinical regimen. At the embryo/foetal no-observed-adverse-effect-level (NOAEL) of 0.6 mg/kg/day, the AUC_{de} was 72 times higher than in humans treated with the clinical regimen.

In the studies in rats, as doses of 1.0 mg/kg/day or higher produced abortions, lower doses were chosen in the following studies for evaluation of dose-response relationships. In the definitive embryo/foetal toxicity study in pregnant female rats, localised alopecia and abortions were observed. The maternal NOAEL was 0.3 mg/kg/day. In the perinatal/postnatal development study in pregnant rats, no overt maternal toxicity was observed in any dosage group. At doses of 0.3 mg/kg/day or more, gestation and perinatal development was affected, in that gestation length was reduced, there were late resorptions and foetal death, postnatal mortality and reduced pup body weight.

The different reproduction toxic effects seen in rats and the lack of foetuses for evaluation in rabbits may be related to the exaggerated pharmacological effect of bimatoprost. Prostaglandin analogues are known to have profound effects on the female reproductive system of mammals. However, *in vitro* studies showed that bimatoprost does not act through the $PGF_{2\alpha}$-sensitive (FP) receptor. *In vitro* studies also showed that where rabbit isolated uteri were extremely sensitive to bimatoprost, isolated human and rodent myometrium were found to be unresponsive to bimatoprost, indicating that bimatoprost sensitive receptors do not mediate uterine contractions in rodents and humans.

However, the metabolite 17-phenyl trinor PGF2α (AGN 191522) does activate the classical FP receptor and induces contractions in isolated mouse, rat, and rabbit uteri and in human myometrium. The metabolite is found in considerable levels in mice, rats and rabbits. It is argued that humans do not produce this metabolite following ocular dosing, and therefore the reproduction toxicity risk would be negligible in humans treated ocularly. In the clinical trials, metabolism to 17-phenyl trinor PGF2α was not detected in women treated ocularly with bimatoprost for 14 days, and bimatoprost incubated in human blood also did not convert to this metabolite. It might therefore be that bimatoprost poses no abortion risk in humans. The abortions seen in mice and rat studies may either reflect the non-selective activation of FP receptors because of high doses given or the selective activation by the metabolite 17-phenyl trinor $PGF_{2\alpha}$.

Genotoxicity

The standard battery of genotoxicity tests showed no evidence of genotoxic potential. Bacterial reverse mutation assays in *S. typhimurium* and *E. coli* were negative. Similarly, the mouse lymphoma assay, mouse micronucleus assay as well as the mouse bone marrow micronucleus test all gave

negative results. The results of these *in vitro* and *in vivo* mutagenicity tests indicate that bimatoprost is not genotoxic.

Immunotoxicity studies

The potential antigenicity of bimatoprost was evaluated with a passive cutaneous anaphylaxis assay (PCA) in mice, rats and guinea pigs and a systemic anaphylaxis assay in guinea pigs. The potential for a delayed dermal contact hypersensitivity response to bimatoprost was examined in guinea pigs. Bimatoprost when administered topically or intradermally did not elicit a dermal sensitisation response. The studies indicate that skin contact with bimatoprost should not induce a hypersensitivity response.

Environmental risk assessment

Risk characterisation calculations have been conducted, showing that the Predicted Environmental Concentration (PEC) of bimatoprost falls below the threshold values for water, soil and grassland. On the background of the calculations, it was considered that the environmental impact of the PEC's will be insignificant associated with use and disposal of the product by the users.

Post authorisation studies

The MAH submitted the results of two 104-day carcinogenicity studies, one in rats and one in mice, as part of the application for first line therapy.

In both mice and rats, systemic absorption and exposure was demonstrated at oral dosing in the carcinogenicity studies. Exposure margins when compared to human dosing were large.

The overall conclusion of the carcinogenicity studies in rats and mice was that there was no evidence of a tumorigenic potential of bimatoprost and section 5.3 "Preclinical safety data" of the Summary of Product Characteristics was updated accordingly.

4. Part IV: Clinical aspects

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Despite its chemical similarity, bimatoprost exhibits a pharmacological profile different from that of prostaglandin $F_{2\alpha}$. Hence, it does not produce pharmacological effects typical of those mediated through prostanoid receptors, e.g. the FP receptor. The lack of prostanoid activity has been explained by the substitution of the carboxylic group in $PGF_{2\alpha}$ with an electrochemically neutral chemical substituent. Instead, bimatoprost appears to mimic the actions of a naturally occurring substance, prostamide $F_{2\alpha}$. This agent is derived from anandamide involving the cyclooxygenase 2 (COX-2) enzyme. The pathway is believed to result in biosynthesis of lipid amides that lower the IOP and can be viewed as acting parallel to the arachidonic acid cascade leading to synthesis of prostaglandins.

Bimatoprost reduces IOP by increasing uveoscleral and trabecular outflow. It is intended for ocular administration as eye drops, solution 0.3 mg/ml. The recommended dose is one drop in the affected eye(s) once daily. The initial approved indication read: "Lumigan is indicated for the reduction of elevated IOP in chronic open angle glaucoma and ocular hypertension as 1. monotherapy in patients: insufficiently responsive to first-line therapy, intolerant or contraindicated to first line therapy, 2. adjunctive therapy to beta-blockers".

Following a Type II variation, the indication was amended to first-line and reads as follows: Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers).

Clinical pharmacology

Pharmacodynamics

- Mechanism of action

192024-011: The mechanism of action of bimatoprost in terms of ocular hypotensive effect was studied in a randomised, double-blind placebo controlled paired comparison in healthy volunteers. Bimatoprost 0.3% ophthalmic solution, and vehicle in the contralateral eye, was administered once daily in the evening for 3 days. The study population included 27 healthy volunteers with an IOP at prestudy visit greater than or equal to 12 mmHg and less than or equal to 21 mmHg in both eyes and less than 2 mmHg asymmetry in the two eyes. IOP was measured at regular intervals. In order to evaluate the mode of action of this ophthalmic preparation, aqueous humour flow, tonographic outflow resistance and apparent outflow resistance (IOP/aqueous humour flow) were measured.

The mean baseline IOPs were similar between the eyes assigned to receive bimatoprost and the eyes assigned to receive vehicle (13.8 and 13.7 mmHg, respectively). On day 4, the mean IOP was decreased in the bimatoprost treated eyes compared to the vehicle treated eyes. Postdosing, IOP was statistically significantly lower ($p<0.001$) in the bimatoprost–treated eyes than in the vehicle-treated eyes. On day 3, the daytime aqueous humour flow was higher in the bimatoprost treated eyes than in the vehicle-treated eyes. On day 4, the night-time aqueous humour flow was also higher in the bimatoprost treated eyes compared to the vehicle-treated eyes. On day 3, mean tonographic outflow resistance was lower in the bimatoprost-treated eyes than in the vehicle-treated eyes. On day 3, mean apparent outflow resistance was lower in the bimatoprost-treated eyes than in the vehicle-treated eyes. On day 4, mean apparent outflow resistance was still significantly lower in the bimatoprost treated eyes than in the vehicle-treated eyes.

From these results it can be concluded that the mechanism of action of bimatoprost appears to be that of outflow enhancement. Tonographic data and calculated values of apparent outflow resistance demonstrated a significant decrease, approximately 30-35%, in outflow resistance in bimatoprost-treated as compared to the vehicle-treated eyes. The reduction of apparent outflow resistance, a parameter that can be measured reliably, is typical of ocular hypotensive drugs that act on the ocular outflow rather than on the ocular inflow system. The ocular hypotensive effect of bimatoprost appears to result from an enhancement of both major routes of aqueous humour outflow, namely trabecular meshwork and the pressure-insensitive uveoscleral outflow routes.

Pharmacokinetics

- General:

Four human pharmacokinetic studies and additional therapeutic drug monitoring in the two phase III monotherapy studies had been conducted by the applicant to characterise the pharmacokinetics of bimatoprost in either healthy subjects or patients with glaucoma or ocular hypertension. In these studies, a total of 81 healthy, normal subjects and 179 patients have been exposed to bimatoprost. The studies are: A single dose intravenous study determining the pharmacokinetics and mass balance of radiolabelled bimatoprost *(study 192024-005)*, two multiple dose studies describing the pharmacokinetic profiles of bimatoprost following once and twice daily ocular dosing for 14 days *(studies 192024-006, 192024-007)*, a multiple dose study comparing the pharmacokinetic profiles of bimatoprost in elderly (≥ 65 years) versus the young subjects after once daily ocular dosing for 7 days *(study 192024-012)*, and two therapeutic drug monitoring studies, as part of the monotherapy Phase III trials *(studies 192024-008, 192024-009)*, characterising the systemic exposure of bimatoprost in patients with glaucoma or ocular hypertension.

Validated, highly sensitive, and selective liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were used to determine bimatoprost and AGN 191522 concentrations in the blood for human pharmacokinetic studies *(Reports PK-00-004 and PK-98-007)*.
In addition, in vitro studies were conducted to characterise ocular tissue penetration and metabolism of bimatoprost. Nearly all of the distribution and metabolism studies were conducted using radiolabelled material, while the absorption studies utilised controlled and traceable product formulations for dosing, and LC-MS/MS detection for determination of drug concentrations in blood and plasma

Absorption

Bimatoprost penetrates the human cornea and sclera well *in vitro*. After one drop of 0.03% ophthalmic solution was administered once daily to both eyes of 15 healthy subjects for 14 days, blood bimatoprost concentrations were below the lower limit of quantitation (0.025 ng/ml) in most subjects within 1 to 1.5 hours after dosing. Mean bimatoprost C_{max} values were similar on days 7 and 14. The mean $AUC_{0\text{-}24\ hr}$ values were also similar on days 7 and 14, indicating that a steady systemic exposure to bimatoprost had been reached during the first week of ocular dosing *(Study 192024-006, report PK-98-119)*.

After one drop of 0.03% ophthalmic solution was applied twice daily to both eyes of 15 healthy subjects for 14 days, blood concentrations of bimatoprost were below the lower limit of quantitation within 2 to 3 hours after dosing. The mean C_{max} and $AUC_{0\text{-}12\ hr}$ values were similar on days 7 and 14 indicating that, as with once daily dosing, a steady systemic exposure to bimatoprost had been reached during the first week of ocular dosing. The mean C_{max} values following the morning dose were 20 to 60% higher than those following the evening dose *(Study 192024-007, report PK-99-040)*.

The effect of age on systemic exposure was investigated after ophthalmic doses of bimatoprost 0.03% were applied twice daily to the eyes of 22 young and 23 elderly subjects for 7 days. The mean $AUC_{0\text{-}24\ hr}$ value of 0.0634 ng·hr/ml in elderly subjects was statistically significantly higher than that of 0.0218 ng·hr/ml in young subjects, suggesting the existence of an age effect. However, this finding is not considered clinically relevant, as in both the elderly and the young C_{max} and $AUC_{0\text{-}t}$ values for days 1 and 7 were not statistically different, indicating that there was no accumulation of bimatoprost in the blood over time. Furthermore, bimatoprost exhibits similar safety and efficacy profiles in both the young and elderly populations without any notable differences in IOP-lowering effects *(Study 192024-012, report PK-00-065)*.

The blood concentrations of bimatoprost from patients with glaucoma or ocular hypertension in the two monotherapy Phase III safety and efficacy studies were measured at selected sites. Seventy-four patients from 192024-008 study and 105 patients from 192024-009 study were subject to pharmacokinetic evaluation. Bimatoprost blood concentrations were similar to those observed in normal, healthy subjects and the expert comments that there was no systemic drug accumulation seen over time *(Study 192024-008, 192024-009, reports PK-00-119 and PK-00-120)*. The AGN 191522 (the potentially pharmacologically active C-1 acid metabolite of bimatoprost) was typically not measurable in blood samples from these studies.

Distribution

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma *(Study 192024-005, report PK-99-001)*. The plasma protein binding of bimatoprost is approximately 88*% (Report PK-99-121)*. Extent of melanin binding was relatively moderate. The *in vitro* binding of bimatoprost to synthetic melanin was ~20% at concentrations of 0.2 – 100 µg/mL. The overall extent of melanin binding was not dependent on concentration, and the binding was reversible *(Report PK-99-045)*. Extent of melanin binding was relatively low.

Metabolism

Bimatoprost is not extensively metabolised before it reaches the systemic circulation *(Report BIO-95-087)* and it is the major circulating species in the blood once it reaches the systemic circulation following conjunctival dosing. Bimatoprost then undergoes glucuronidation, hydroxylation, N-deethylation and deamidation to form a diverse variety of metabolites. The glucuronide conjugates of bimatoprost are the most abundant metabolite excreted in urine and faeces. Due to extremely low drug systemic concentrations of bimatoprost (less than 0.2 ng/mL) following ocular dosing, no systemic drug-drug interactions are anticipated (Reports PK-95-013, PK-97-004, PK-99-037, PK-99-113 and PK-99-047).

Excretion

Following an intravenous dose of radiolabelled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of total radioactivity was 14.5 ng-eq/mL. Total radioactivity was eliminated from the body with a short half-life of 1.74 hours. The blood concentration of intact

bimatoprost was 12.2 ng/mL at maximum and declined rapidly with an elimination half-life of 0.771 hr. Blood concentrations of AGN 191522, the C-1 acid metabolite, were much lower than those of bimatoprost with the peak concentration of 0.12 ng/mL. The total blood clearance (Cl_b) of unchanged bimatoprost was 1.50 L/hr/kg (Study 192024-005, report PK-99-001). Sixty-seven percent of the administered dose of bimatoprost was excreted in the urine with only a small fraction excreted as unchanged drug. Twenty-five percent of the dose was recovered in faeces of which 15-40% was eliminated as unchanged drug (Study 192024-005, report PK-99-001). The renal clearance of bimatoprost has not been determined.

- Interaction studies:

In vivo drug-drug interaction studies in animals or in humans have not been performed. This could be considered acceptable because extremely low drug concentration of the parent drug (less than 0.2 ng/mL) was observed in the systemic circulation in humans following multiple ocular dosing of the 0.03% solution. AGN 191522 (the C1 acid metabolite) concentration was typically not measurable and consequently, it is unlikely that blood concentrations of bimatoprost or AGN 191522 would be increased to clinically relevant levels. Secondly, multiple enzymes and pathways are involved in the metabolism of bimatoprost rather than a single major one and the possibility for a clinically significant drug-drug interaction to take place is therefore very small. This conclusion could be supported by the lack of drug effects on hepatic drug metabolising enzymes in rats and monkeys following one month of i.v. administration.

Clinical efficacy

The clinical trials were performed according the Code of Federal Regulations and the relevant Good Clinical Practice Guidelines and the studies were performed according to the Declaration of Helsinki.

Dose-response studies and main clinical studies

Dose response studies

Four studies (192024-001, -002, -003, -004) were conducted. The study populations were similar and included patients with open angle glaucoma and ocular hypertension, with an IOP at 8 a.m. ≥23 to ≤34 mmHg.

-001: In this study different concentrations of non-preserved bimatoprost 0.01%, 0.03% and 0.1%, were compared to timolol 0.5% and vehicle, all in a bid regimen. Study drugs were instilled for 5½ days and the effect was evaluated on days 0, 1, 2, 3, 5, 6, and 7. A total of 60 patients with a mean age of 59.6 years (31-79) with a M:F ratio of 20:40 were studied. Baseline IOP's at H0 were similar: 24.25-27.79 mmHg. All active groups had a statistically significant mean decrease compared to baseline at all hours (0, 1, 2, 4, 6). The 0.03% and the 0.1% groups had a greater percentage decrease than timolol, and a duration of 24 hours of the effect was indicated.

-002: In this study bimatoprost non-preserved 0.003%, 0.01%, 0.03% qd in the evening for 3 weeks, followed by bid for one week, and vehicle, and timolol 0.5% bid was studied in a population of 100 patients. The mean age was 59.9 years (37-90) with the M:F of 46:54. IOP was evaluated pre-study, day 0, 3, 7, 14, 21, 23, 28, and 30. The values H0, H4, H8, H12, H14 were evaluated on days 0, 21, and 28. On day 14 H0, H8, and H12 values were evaluated. For the diurnal observations at day 21 (end of qd dosing), at all timepoints 0.03% had greater effect than the other bimatoprost groups, and this group had a statistically significantly greater mean decrease than timolol. For the diurnal observations at day 28 (end of bid dosing), the results are very similar to those at day 21. The hypotensive effect of 0.01% and 0.03% qd was greater than with timolol 0.5% and with vehicle.

-003: The efficacy of preserved bimatoprost 0.03% versus vehicle was studied in a qd morning dose regimen of one months duration. A number of 32 patients with a mean age of 57.5 years (27-83) and a M:F ratio of 10:22 were included. IOP evaluation took place at day 0, 1, 14, 28 and 29. The baseline IOP was similar: 21.1 mmHg in the bimatoprost group and 24.9 mmHg in the vehicle group. It could be concluded that the mean H0 decrease in IOP from baseline was statistically significant in both bimatoprost 0.03% and the vehicle group. A statistically significant difference between the active

group and the vehicle group was obtained at day 14 and 29, but not on day 28. Mean diurnal IOP decrease was significantly greater with bimatoprost 0.03% than with vehicle at H4 and H8, but not at H0 and H12 on day 28.

-004: In this study preserved (P) bimatoprost 0.03%, non-preserved (NP) bimatoprost 0.03%, AGN 0.06% (another IOP decreasing compound), latanoprost 0.005% and vehicle were studied in a qd evening dosing regimen for one month. A number of 106 patients with a mean age of 65.6 years (41-85), and a M:F ratio of 41:65 was studied. Determination of IOP was performed pre-study at day 0, 14, and 29. IOP at baseline was similar in the study groups: 24.7-25.9 mmHg. At day 29 the difference in decrease in IOP at H0 was statistically significant between all active groups and vehicle; no statistical significance between the active groups was found. It could be concluded that the IOP decreasing effect of both P and NP bimatoprost 0.03% and latanoprost, qd in an evening dose regimen was clinically and statistically significantly superior to vehicle. No statistically significant difference between the active groups was observed.

Main studies

The phase 3 clinical programme included 2 pivotal trials with identical protocols, 192024-008 and 192024-009, in which bimatoprost 0.03% in monotherapy was compared to timolol 0.5%. Bimatoprost was applied once, in the evening, or twice daily, and timolol was applied in a twice daily regimen. The initial dossier provided data from the first 6 months of these planned 12 months studies. In 2 other pivotal studies bimatoprost 0.03% was administered adjunctively to a beta-blocker and was compared to bimatoprost vehicle/beta-blocker: Study 192024-502, and to latanoprost 0.005%/beta-blocker: Study 192024-501, respectively. The two adjunctive studies were both of 3 months duration, and 12 months data were subsequently provided for the -501 study. A once and a twice daily bimatoprost 0.03% regimen were compared to vehicle, in combination with any beta-blocker in a twice daily regimen. Bimatoprost qd or bid was compared to latanoprost qd (the approved posology), both in conjunction with any beta-blocker applied bid As part of the Response to the List of Questions, 12 months data for the monotherapy studies and 12 months data for the adjunctive therapy study (502) were submitted, as well as two new studies.

STUDY 192024-008

Description of the study

Multicentre, double-masked, randomised, parallel, three month study (with treatment extended to one year) of the safety and efficacy of bimatoprost 0.03% ophthalmic solution administered once daily or twice daily compared with timolol 0.5% ophthalmic solution administered twice daily in subjects with glaucoma or ocular hypertension.

The diagnoses of the patients were ocular hypertension, chronic open-angle glaucoma, chronic angle–closure glaucoma with patient iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma, requiring bilateral treatment. The inclusion criteria were patients aged more than or equal to 21 years, day 0 (post-washout) intraocular pressure (IOP) more than or equal to 22 mmHg to less than or equal to 34 mmHg in each eye by applanation tonometry and best-corrected visual acuity (VA) more than or equal to 20/100 in each eye. Mean change from baseline IOP was the primary efficacy variable. Patient satisfactory questionnaire and clinical success evaluation were also evaluated.

Statistical analysis

The data from the worse eye were analysed in terms of observed values and changes from baseline at each follow-up visit. Intent-to-treat (ITT) with last observation carried forward (LOCF) was used for the analysis of IOP. All randomised patients were included and, for those patients who discontinued prior to the month 6 visit for any reason, their last observed data was carried forward in the analysis to subsequent timepoints. LOCF was also applied to patients who continued in the study but missed the month 6 visit. Missing data between visits were not imputed. A per protocol analysis on observed cases was also performed for IOP. Only patients who met the entry criteria, had no major protocol violations, received study medication, had at least 1 follow-up visit, and visits within specified time windows were included in this analysis.

Diurnal IOP was measured at each visit (ideally between 7:30 AM and 8:30 AM but 7:00 AM to 9:00 AM was acceptable), and at 2 and 8 hours after hour 0. A strategy of combined tests of non-inferiority and statistical superiority was employed. For each comparison of the differences in the IOP reduction from baseline between 2 treatment groups, a δ=1.5 mmHg was used as the non-inferiority margin. In addition, within each treatment group, mean IOP changes from baseline were analysed using paired t-tests.

RESULTS

Study populations/accountability of patients

The population consisted of 602 subjects. The age range for the ITT population was from 22 to 90 years with fewer males (46%) than female subjects (54%). 50% of the population had a primary diagnosis of open-angle glaucoma, 47% of ocular hypertension and 3% were mixed (ocular hypertension in one eye and open-angle glaucoma in the other). The population was primarily Caucasian (76.7%). The most common iris colours were brown (36.9%) and blue (24.6%). There were no statistically significant differences among the 3 treatment groups with regard to demographics or baseline characteristics.

There were 602 patients enrolled in the study, 240 patients randomised to bimatoprost qd, 240 were also randomised to bimatoprost bid and 122 were randomised to timolol. In the ITT analysis 96.0% of patients completed 2 weeks of treatment, 93.9% of patients completed 6 weeks, 88.7% of patients completed 3 months, and 85.7% (535/596) completed 6 months. The most frequent reason for discontinuation of the study up to month 6 was adverse events (11.1%). Only 8 patients discontinued up to month 6 due to lack of efficacy: 0% patients in the bimatoprost qd group, 2.5% patients in the bimatoprost bid, and 1.6% patients in the timolol group. Only data from the worse eye was analysed, the worse eye being defined as that eye with the greater IOP at baseline or, if the IOP was equal in both eyes, the right eye.

Efficacy results

Data on 6 months of treatment was initially provided. There were no differences with respect to baseline IOP among the three groups. At the primary endpoint, the mean change from baseline to hour 0 of month 6 was 7.88 mmHg for those patients receiving bimatoprost 0.03% qd, 7.00 mmHg for those receiving bimatoprost 0.03% bid and 6.27 mmHg in the timolol group. The bimatoprost once daily results were superior to those achieved by the timolol group ($p<0.001$) whilst the bimatoprost 0.03% twice daily was non-inferior to timolol. In addition, the IOP lowering seen with once daily dosing group was superior to the twice daily dosing group at the primary endpoint. These analyses gave the same results for both the ITT population and the Per Protocol (PP) population.

Overall, at month 6, the mean decreases from baseline in IOP at hours 0, 2 and 8 in patients treated with bimatoprost once daily in the ITT population ranged from 6.88 to 7.88 mmHg. These were significantly ($p<0.001$) greater than those achieved in patients treated with timolol (4.17 to 6.27 mmHg). The twice daily bimatoprost results were superior to the timolol results at month 6 only at hour 8 ($p<0.007$) and non-inferior at the other two time points hours 0 and 2. Efficacy remained consistent at all timepoints evaluated. For the bimatoprost once daily group, mean decreases from baseline at hours 0, 2 and 8 were superior to timolol ($p<0.001$) at all visits with the twice daily dosing

results being non-inferior to timolol results at all visits. Again, the PP population results were similar to those seen with the ITT population.

STUDY 192024-009

Description of the study

Multicentre, double-masked, randomised, parallel, three month study (with treatment extended to one year) of the safety and efficacy of bimatoprost 0.03% ophthalmic solution administered once daily or twice daily compared with timolol 0.5% ophthalmic solution administered twice daily in subjects with glaucoma or ocular hypertension. The inclusion and exclusion criteria were the same as for study 192024-008. Mean change from baseline IOP was the primary efficacy variable. Patient satisfactory questionnaire and clinical success evaluation were also evaluated. Safety measures and statistical analysis were the same as in study 008.

RESULTS

Study populations/accountability of patients

The population consisted of 596 subjects. The age range for the ITT population was from 26 to 92 years with fewer males (44%) than female subjects (56%). 62.6% of the population had a primary diagnosis of open-angle glaucoma, 36.6% of ocular hypertension and only 0.8% were mixed (ocular hypertension in one eye and chronic glaucoma in the other). The population was primarily Caucasian (74.7%). The most common iris colours were brown (35.9%) and blue (22.0%). There were no statistically significant differences among the 3 treatment groups with regard to demographics or baseline characteristics.

Of the enrolled patients 234 were randomised to bimatoprost qd, 243 were randomised to bimatoprost bid, and 119 were randomised to timolol. In the ITT analysis, 96.5% of patients completed 2 weeks of treatment, 94.5% of patients completed 6 weeks, 92.1% of patients completed 3 months, and 89.8% (535/596) completed 6 months. The most frequent reason for discontinuation of the study up to month 6 was adverse events (5.9%). Only 9 patients discontinued up to month 6 due to lack of efficacy: 2 (0.9%) patients in the bimatoprost qd group, 3 (1.2%) patients in the bimatoprost bid, and 4 (3.4%) patients in the timolol group.

Efficacy results

Data on 6 months of treatment was initially provided. There were no differences with respect to baseline IOP among the three groups. At the primary endpoint, the mean change from baseline at hour 0 of month 6 was 8.69 mmHg for those patients receiving bimatoprost 0.03% qd, 7.30 mmHg for those receiving bimatoprost 0.03% bid and 6.63 mmHg in the timolol group. As for the preceding study the bimatoprost once daily results were superior to those achieved by the timolol group with the bimatoprost 0.03% twice daily being non-inferior to timolol. As with the previous study, the IOP lowering seen with once daily bimatoprost dosing group was superior to the twice daily dosing group at the primary endpoint. These analyses were the same for both the ITT population and the PP population. Overall, at month 6, the mean decreases from baseline in IOP at hours 0, 2 and 8 in patients treated with bimatoprost once daily in the ITT population ranged from 7.14 to 8.69 mmHg. These were significantly ($p<0.001$) greater than those achieved in patients treated with timolol (4.96 to 6.63 mmHg). The twice-daily bimatoprost results were superior to results achieved with timolol only at hour 8 and non-inferior at the other two time points. Efficacy again remained consistent at all timepoints evaluated. For the bimatoprost once daily group, mean decreases from baseline at hours 0, 2 and 8 were superior to timolol at all visits with the twice daily dosing results showing superiority to timolol at 8 of the 12 time points measured in the study. Again, the PP population results were similar to those seen with the ITT population.

STUDY 192924-008 AND -009 12 MONTH DATA

The 12-months data from both study 008 and 009 (submitted as part of the response to List of Questions) confirm a consistent IOP-lowering effect with bimatoprost 0.03% eye drops qd in patients

with chronic open angle glaucoma or ocular hypertension. In comparison with timolol 0.5% eye drops bid bimatoprost qd was superior at all visits at all measured timepoints (H0, H2 and H8, the number of H12 values was too small for statistically meaningful comparison). The number and percentage of patients who obtain the clinically relevant IOP at or below 17 mmHg at 8 a.m. (=12 hours post dose) is consistently greater with bimatoprost qd than with timolol. Furthermore, the results confirm the choice of the once daily dosing regimen with bimatoprost 0.03% as appropriate.

STUDIES 192924-010 AND –016

In addition to the above-mentioned, pivotal trials, the company has submitted (as part of the response to List of Questions) two new studies:

Study 010: This was an investigator-masked, randomised, multi-centre, parallel group comparison of bimatoprost 0.03% and latanoprost 0.005% applied once daily for 3 months in patients with open angle glaucoma or ocular hypertension. The study demonstrated that the IOP decreasing effect of bimatoprost was non-inferior to that of latanoprost at all measured time points through the 3 months treatment period. The proportion of patients who achieved an hour 0 IOP of less than or equal to 17 mmHg was at each visit greater with bimatoprost than with the comparator. This parameter was not defined prior to the study, but is clinically relevant.

Study 016: This was a randomised, investigator-masked parallel group comparison of the safety and 24-diurnal efficacy of bimatoprost 0.03%, timolol gel 0.5% and latanoprost 0.005%, applied once daily. For the diurnal control of IOP bimatoprost administered in the evening was generally superior to a timolol gel preparation administered in the morning, and, with few exceptions, non-inferior to latanoprost, administered in the evening in patients with open-angle glaucoma or ocular hypertension in a one month study.

Phase III-Adjunctive studies

Two phase III studies have been performed to investigate bimatoprost 0.03% as adjunctive therapy to beta-blockers in patients not adequately controlled on topical beta-blockers. A total of 722 patients were enrolled of whom 246 patients instilled bimatoprost 0.03% qd, 243 patients instilled bimatoprost 0.03% bid, 138 patients instilled latanoprost 0.005% qd, and 95 patients instilled vehicle bid, each adjunctively with a topical beta-blocker bid. The inclusion and exclusion criteria for each study were comparable to those employed in the monotherapy programme.

Study 192024-501

Description of the study

Multicentre, investigator-masked, randomised, parallel-group design to evaluate the safety and efficacy of bimatoprost 0.03% ophthalmic solution administered to each eye once daily in the evening or twice daily compared with latanoprost 0.005% ophthalmic solution administered to each eye once daily in the evening. The study medications were given adjunctively with a topical beta-blocker bid for 3 months. The inclusion criteria were adult patients diagnosed with ocular hypertension, chronic open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative glaucoma, or pigmentary glaucoma, investigator masked requiring bilateral treatment and with an elevated IOP inadequately controlled on beta-blocker alone. The exclusion criteria were comparable to those employed in the monotherapy studies but in this case the patients wearing contact lenses were excluded since use of all contact lenses is contraindicated for latanoprost. IOP was the primary efficacy variable. The primary endpoint was change from baseline IOP at hour 0, month 3.

Statistical analysis

The statistical plan clearly stated that all other timepoints would be analysed and would contribute to the final product evaluation. As in the two monotherapy studies intent-to-treat (ITT) with last observation carried forward (LOCF) was used for the analysis of IOP. All randomised patients were included, and last observed data was carried forward in the analysis to subsequent timepoints for the

patients who for any reason discontinued prior to the month 3 visit. Only patients who met the entry criteria, had no major protocol violations, received study medication, had at least 1 follow-up visit, and visits within specified time windows were included in this analysis. Diurnal IOP was measured at each visit (ideally between 08:30 AM and 10:30 AM), and at 2 and 8 hours after hour 0. A strategy of combined tests of non-inferiority and superiority was employed. For each comparison of the differences in the IOP reduction from baseline between 2 treatment groups, δ=1.5 mmHg was used as the non-inferiority margin. A hierarchical procedure was used for the pairwise comparisons. In addition, within each treatment group, mean IOP changes from baseline were analysed using paired t-tests.

RESULTS

Study populations/accountability of patients

The population consisted of 437 subjects. The age range for the ITT population was from 22 to 90 years with fewer males (40%) than female subjects (60%). 85% of the population had a primary diagnosis of chronic glaucoma, 15% of ocular hypertension. The population was primarily Caucasian (94.7%). The most common iris colours were brown (37.3%) and blue (18.1%).

The patients were required to use the beta-blocker chosen by the investigator and this was to be maintained throughout the duration of the study. The most commonly used beta-blocker was timolol (55.6% of patients). Other beta-blockers used were levobunolol (24.3%), betaxolol (16.0%), carteolol (3.9%) and metipranolol in 0.2% of patients. Thus, the adjunctive treatment was a cardioselective beta-blocker for 16% of patients, and a non-selective beta-blocker for 84% of patients.

Of the 437 enrolled patients 153 were randomised to bimatoprost qd/beta blocker, 146 were randomised to bimatoprost bid/beta blocker and 138 were randomised to latanoprost/beta-blocker. The ITT populations included all randomised patients 437 patients. The PP population included 90.6% (396/437) of enrolled patients: 138 patients in the bimatoprost qd/beta-blocker group, 130 patients in the bimatoprost bid/beta-blocker group, and 128 patients in the latanoprost/beta-blocker group. The most frequent reason for discontinuation of the study was adverse events (3.7%). Only 1 patient discontinued due to lack of efficacy, in the latanoprost/beta-blocker group.

Efficacy results

There were no differences with respect to baseline IOP (ie, IOP following minimum of 3 weeks run-in on beta-blocker) among the three groups. The mean change from baseline at hour 0 of month 3 (the primary end-point) was 7.95 mmHg for those patients receiving once daily bimatoprost 0.03% with beta-blocker. This value was 7.26 mmHg for those receiving bimatoprost 0.03% twice daily/ beta-blocker and 7.35 mmHg in the latanoprost/beta-blocker group. The mean change from baseline in both bimatoprost/beta-blocker groups was non-inferior to that achieved by the latanoprost/beta-blocker group. The PP population analysis showed the bimatoprost qd/beta-blocker group to be non-inferior to the latanoprost/beta-blocker group but this was not achieved by the bimatoprost bid/beta-blocker group.

Overall, at month 3, the mean decreases from baseline in IOP at hours 0, 2 and 8 in patients treated with bimatoprost qd/beta-blocker in the ITT population ranged from 6.03 to 7.95 mmHg. These were non-inferior to the decreases seen in the latanoprost/beta-blocker group (5.89 to 7.35 mmHg) at all time points. These conclusions were confirmed by the PP analysis. Mean changes from baseline hour 0 IOP across all follow-up visits ranged from -7.23 to -7.95 mmHg with bimatoprost qd/beta-blocker, and from -6.91 to -7.53 mmHg with latanoprost/beta-blocker. The decreases from baseline hour 0 IOP were statistically significant within each treatment group at each follow-up visit ($p<0.001$).

The bimatoprost bid/beta-blocker group mean decreases from baseline IOP at month 3 ranged from 4.64 to 7.26 mmHg at all the diurnal time points. Non-inferiority was not achieved at the hour 2 or 8 time points in either the ITT or the PP populations and not at hour 0 for the PP as already noted.

Efficacy remained consistent at all the time points evaluated over the 3-month period in each treatment group. For the bimatoprost qd/beta-blocker group, mean decreases from baseline at hours 0 and 2 were non-inferior to latanoprost/beta-blocker at all visits. At hour 8, week 4 non-inferiority was not

achieved but was present at weeks 2 and 8 and month 3. The bimatoprost bid/beta-blocker group results did not show non-inferiority with respect to the latanoprost/beta-blocker group at hours 2 and 8 at any visit but non-inferiority was achieved at all visits for the hour 0 result.

In keeping with the statistical plan comparisons of the bimatoprost qd/beta-blocker and bimatoprost bid/beta-blocker regimens at hour 0 could only be performed. This showed the once daily to be non-inferior to the twice daily regimen when used adjunctively with beta-blocker (confirmed by the PP analysis).

Study 192024-502

Description of the study

Multicentre, double-masked, randomised, parallel-group design to evaluate the safety and efficacy of bimatoprost 0.03% ophthalmic solution administered to each eye once daily in the evening or twice daily compared with vehicle administered to each eye twice daily. The study medications were given adjunctively with a topical beta-blocker bid for 3 months. Masked treatment continued for a further 9 months. However, all patients who had received vehicle in the first 3 months were randomised to receive one of the active treatment regimens in combination with beta-blocker in the extension phase. The inclusion and exclusion criteria, the primary endpoint, safety measures and statistical analysis were similar to those described in study 192024-501.

RESULTS

Study populations/accountability of patients

The population consisted of 285 subjects entered by 28 investigators. 93 patients were randomised to the bimatoprost 0.03% qd/beta-blocker group, 97 to the bimatoprost 0.03% bid/beta-blocker group and 95 to the vehicle/beta-blocker group. The age range for the ITT population was from 22 to 87 years with fewer males (46.7%) than female subjects (53.3%). In the ITT population, the entry diagnosis was chronic glaucoma for approximately 90% of patients and OHT for approximately 10%. The population was primarily Caucasian (91.6%). The most common iris colours were brown (39.3%) and blue (15.1%). There were no significant differences among the 3 treatment groups in any baseline characteristic.

The patients were required to use the beta-blocker chosen by the investigator and this was to be maintained throughout the duration of the study. The most commonly used beta-blocker was timolol (54.7% of patients). Other beta-blockers used were levobunolol (22.5%), betaxolol (20.7%), carteolol (2.1%) and metipranolol in 0.7% of patients. Thus, the adjunctive treatment was a cardioselective beta-blocker for 20% of patients, and a non-selective beta-blocker for 80% of patients. The ITT populations included all randomised patients: 285 patients. The PP-populations included 93.0% (265/285) of randomised patients. The most frequent reason for discontinuation of the study prior to month 3 was AEs (6.7%, 19/285). Only 0.4% (1/285) of patients discontinued prior to month 3 due to lack of efficacy. This patient was in the vehicle/beta-blocker group.

Efficacy results

There were no differences with respect to baseline IOP among the three groups. The mean change from baseline at hour 0 of month 3 (the primary end-point) was 7.38 mmHg for those patients receiving once daily bimatoprost 0.03% with beta-blocker. This value was 6.34 mmHg for those receiving bimatoprost 0.03% twice daily/ beta-blocker and 3.59 mmHg in the vehicle/beta-blocker group. The mean change from baseline in both bimatoprost/beta-blocker groups was superior to that achieved by the vehicle/beta-blocker group. The PP population analysis confirmed these results.

Overall at month 3 the mean decreases from baseline in IOP at hours 0, 2 and 8 in patients treated with bimatoprost qd/beta-blocker in the ITT population ranged from 6.39 to 7.38 mmHg. These were superior to the decreases seen in the vehicle/beta-blocker group (2.62 to 3.59 mmHg) at all time points. Mean decreases from baseline hour 0 IOP across all follow-up visits ranged from 6.53 to 7.38 mmHg with bimatoprost qd/beta-blocker, and from 2.04 to 3.59 mmHg with vehicle/beta-blocker. The decreases from baseline hour 0 IOP were superior to those seen in the

vehicle/beta-blocker group at hour 0 at all time points. Superiority of the bimatoprost qd/beta-blocker group results was also seen compared to vehicle/beta-blocker at all time points at all visits.

The bimatoprost bid/beta-blocker group also showed superiority to vehicle/beta-blocker at all time points at all visits. The comparison of the bimatoprost qd/beta-blocker regimen with the bimatoprost bid/beta-blocker regimen showed the qd to be non-inferior at all time points and superior at over 40% of time points with respect to IOP lowering.

Study 192024-502, 9/12 months data:

As part of the response to List of questions the company has submitted 12 and 9 months data on adjunctive therapy (extension study 502). A consistent IOP-decreasing effect of bimatoprost qd adjunctively to a topical beta-blocker was demonstrated in this 12/9 months extension study. Statistically significant changes from 3-months values in the IOP were also seen in those patients who started with vehicle/beta-blocker switched to bimatoprost/beta-blocker regimen.

Clinical studies in special populations

No special studies to investigate clinical efficacy in special populations were undertaken. However, in a pooled analysis of the monotherapy studies 008 and 009, in each of the subgroups age, sex, race, and iris color, the mean decreases in IOP from baseline, over all timepoints and all follow-up visits, in patients treated with bimatoprost qd, were similar to the overall population. This was also the case in patients treated with bimatoprost bid, demonstrating that bimatoprost qd and bimatoprost bid are effective in reducing IOP in each of the subgroups assessed. Similarly, in a pooled analysis of the adjunctive therapy studies 501 and 502, in the subgroups age, sex, and iris colour, the mean decrease in IOP from baseline over all timepoints and all follow-up visits in patients treated with bimatoprost QD/beta-blocker, were similar to the overall population. It was also the case in patients treated with bimatoprost BID/beta-blocker, demonstrating that bimatoprost QD/beta-blocker and bimatoprost BID/beta-blocker are effective in reducing IOP each of these subgroups assessed. The number of black patients in the pooled adjunctive studies was small (4.8%) and the results in this subgroup should be interpreted with caution.

Discussion on clinical efficacy

Dose finding

The 0.03% concentration of bimatoprost ophthalmic solution was chosen for use in the phase III studies based on the results of the phase II dose-response studies. These studies demonstrated that 0.03% provided greater lowering of IOP than either the lower concentrations (0.003%, 0.01%), or the higher concentration (0.1%) of bimatoprost. In the phase II studies it was demonstrated that the lowering of IOP begins within 4 hours of initial instillation of bimatoprost. The ocular hypotensive effect is maintained up to 24 hours post-instillation, suggesting the potential efficacy with qd administration. An evening dosing for the qd regimen was selected for evaluation in the phase III studies so that the time of maximal efficacy of the drug coincided with the morning hours (08:00 to 11:00 AM) when untreated IOP is usually highest. In view of the results obtained in study 192024-002, where bimatoprost bid administration also demonstrated IOP lowering effect, both regimens once daily (qd) and twice daily (bid) were included in the phase III studies to compare their efficacy.

Main studies

Four phase III studies were submitted to support the requested indication. The design of these studies is considered appropriate in this disease and the duration is sufficient to demonstrate the efficacy of the product. The primary endpoint (mean change from baseline IOP) is considered acceptable and clinically relevant.

Monotherapy: Two phase III studies (192024 – 008 and -009) assess bimatoprost 0.03% as monotherapy in the management of patients with chronic glaucoma or ocular hypertension. Both studies follow the same design. The safety and efficacy of bimatoprost 0.03% ophthalmic solution administered to each eye qd in the evening or bid was compared with timolol 0.5% ophthalmic

solution administered to each eye bid. The data initially provided by the applicant included only a period of 6 months of treatment. The results obtained in each study are the following:

Study 008- At the primary endpoint (IOP lowering) the mean change from baseline at hour 0 was 7.88 mmHg after 6 months for those patients receiving bimatoprost 0.03% qd, 7.00 mmHg for those receiving bimatoprost 0.03% bid and 6.27 mmHg in the timolol group. The bimatoprost qd reductions were higher than those achieved in the timolol group ($p<0.001$) while those of bimatoprost 0.03% bid were non-inferior to timolol. In addition, the IOP lowering seen with once daily dosing group was superior to the twice daily dosing group at the primary endpoint. Similar results were obtained for both the ITT population and the PP population.

Study 009- At the primary endpoint (IOP lowering), the mean change from baseline at hour 0 was 8.69 mmHg after 6 months for those patients receiving bimatoprost 0.03% qd, 7.30 mmHg for those receiving bimatoprost 0.03% bid and 6.63 mmHg in the timolol group. As for the preceding study the bimatoprost qd reductions were higher than those achieved in the timolol group with the bimatoprost 0.03% bid being non-inferior to timolol. As with the previous study, the IOP lowering seen with once daily bimatoprost dosing group was superior to the twice daily dosing group at the primary endpoint. Similar results were obtained for both the ITT population and the PP population. The results obtained in both clinical trials confirm that the regimen of posology qd was superior to bid and on the other hand the superiority of bimatoprost 0.03% qd.

The 12-months data from both study 008 and 009 (submitted as part of the response to List of Questions) confirm a consistent decreasing effect on IOP with bimatoprost 0.03% eye drops qd in patients with chronic open angle glaucoma or ocular hypertension. The number and percentage of patients who obtained the clinically relevant lowering of the IOP was consistently greater with bimatoprost qd than with timolol. Furthermore, the results confirm the choice of the once daily dosing regimen with bimatoprost 0.03% as appropriate.

Results of the Study 010 demonstrated that the IOP decreasing effect of bimatoprost was non-inferior to that of latanoprost through the 3 months treatment period. Furthermore, from the results of the one month Study 016 it can be concluded that for the diurnal control of IOP, bimatoprost applied in the evening is generally superior to a timolol gel preparation administered in the morning, and, with few exceptions, non-inferior to latanoprost, applied in the evening in patients with open-angle glaucoma or ocular hypertension.

Adjunctive therapy: Two phase III studies (192024 – 501 and 502) were performed comparing a once daily bimatoprost dosing regimen and bimatoprost twice daily administration but in combination with twice daily topical beta-blocker when the patients were not adequately controlled on topical beta-blockers. The first study evaluates the safety and efficacy of bimatoprost 0.03% ophthalmic solution administered to each eye qd in the evening or bid compared with latanoprost 0.005% ophthalmic solution administered to each eye qd in the evening. The study medications were given adjunctively with a topical beta-blocker bid for 3 months. In the second study, bimatoprost was compared with vehicle administered to each eye twice daily during 3 months and after all the patients were included in the treatment with bimatoprost. The results obtained in each study are the following:

Study 501- The mean decrease from baseline at hour 0 after 3 months (the primary end-point) was 7.95 mmHg for those patients receiving once daily bimatoprost 0.03% with beta-blocker. This value was 7.26 mmHg for those receiving bimatoprost 0.03% twice daily/ beta-blocker and 7.35 mmHg in the latanoprost/beta-blocker group. The mean change from baseline in both bimatoprost/beta-blocker groups was non-inferior to that achieved by the latanoprost/beta-blocker group. The ITT population analysis showed the bimatoprost qd/beta-blocker group to be non-inferior to the latanoprost/beta-blocker group. This was not the case for the bimatoprost bid/beta-blocker group. The PP population analysis confirmed these results.

Study 502- The mean decrease from baseline at hour 0 after 3 months (the primary end-point) was 7.38 mmHg for those patients receiving once daily bimatoprost 0.03% with beta-blocker. This value was 6.34 mmHg for those receiving bimatoprost 0.03% twice daily/ beta-blocker and 3.59 mmHg in the vehicle/beta-blocker group. The ITT population analysis showed that the mean change from baseline in both bimatoprost/beta-blocker groups was superior to that achieved by the vehicle/beta-blocker group. The PP population analysis confirmed these results. The results of the extension of the study 502 showed a consistent IOP-decreasing effect of bimatoprost qd adjunctively to a topical beta-

blocker during the 12/9 months extension. Statistically significant changes from 3-months values in the IOP were also seen in those patients who started with vehicle/beta-blocker switched to bimatoprost/beta-blocker regimen.

Few patients discontinued the phase III studies due to lack of efficacy. In the phase III monotherapy studies, 2 patients (0.4%) treated with bimatoprost qd, and 9 patients (1.9%) treated with bimatoprost bid discontinued due to lack of efficacy, and in the phase 3 adjunctive studies, no patients discontinued due to lack of efficacy.

Extension of indication to first line therapy

The Marketing Authorisation Holder applied through a Type II variation for an extension of indication to first line therapy in the treatment of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers). The MAH submitted the following clinical data: 2-year and 3-year bimatoprost monotherapy versus timolol (Study 192024-014) and 6-month comparative data of bimatoprost monotherapy versus latanoprost (Study 192024-019). In addition, two studies provided supportive data: bimatoprost monotherapy versus a fixed combination (Study 192024-013) and bimatoprost versus adjunctive therapy (Study 192024-015). Furthermore, a review of all available published literature was submitted. This included two papers on the use of bimatoprost in those patients who have failed to respond to latanoprost (Gandolfi & Cimino, 2003; Williams, 2003).

Study 192024-014 (Month 24)

Description of the study

This was an extension of studies 192024–008 and 192024–009. Patients who had completed month 12 in one of these studies were included in this extension, depending on the centre's willingness to participate and on the willingness of the patients' to continue double-blind treatment. The study was double-masked, and the patients continued on the trial medication according to their randomisation at inclusion in the original study. IOP measurements were performed at H0 and H2.

Mean change from baseline (ie IOP at Day 0 in studies 192024-008 and 192024-009) continued to be the primary efficacy variable. A mean decrease in IOP of 3 mmHg from baseline was considered clinically relevant. Mean IOP was a secondary variable. In addition, subjects completed a satisfaction questionnaire using a 7-point scale and the Investigator evaluated his/her willingness to continue the patient on the current medication (assuming that treatment was still required) and that the medication was commercially available. This was called "Pharmacoeconomic evaluation".

The treatment regimens were bimatoprost once daily (vehicle in the morning and active treatment in the evening), bimatoprost twice daily, or timolol 0.5% twice daily, respectively. Since the recommended dosage regimen is once daily, the efficacy data for the bid regimen are not discussed further.

Statistical analysis

ITT with LOCF was used for IOP analysis using data from the worse eye as described for the original 12-month studies.

RESULTS

Study population/accountability of patients

A total of 23 centres in the USA contributed data. The intention to treat (ITT) population encompassed 379 patients with the distribution 167 patients in the bimatoprost qd group, 131 in the bimatoprost bid group, and 81 patients in the timolol group. The demographic and other baseline characteristics were broadly similar in the three groups. As for ocular diagnoses, 61.7% had glaucoma, 36.4% had ocular hypertension, and 1.8% had a mixed diagnosis, i.e. glaucoma in one eye and ocular hypertension in the fellow eye.

Efficacy results

Overall at month 24 the mean decreases from baseline in IOP at hours 0 and 2 in patients treated with bimatoprost once daily in the ITT population ranged from 7.4 to 8.6 mmHg. These continued to be statistically significantly greater ($p<0.001$) than those achieved in patients treated with timolol (4.6 to 6.0 mmHg) at every visit.

As shown in the table below, at H0 the mean change in IOP from baseline ranged from –8.6 to– 8.0 mmHg in the bimatoprost qd group, and from -6.0 to -5.4 mmHg in the timolol group. The mean change with bimatoprost qd was statistically superior to timolol at every visit ($p<0.001$).

As for the H2 results, the mean change ranged from –8.2 to – 7.4 mmHg with bimatoprost qd, and from –5.1 to –4.6 mmHg with timolol. The H2 values also were statistically superior for the bimatoprost qd regimen compared to timolol ($p<0.001$) at all visits with pair wise comparisons.

The mean change in IOP (mmHg) is illustrated in the table below.

Study 192024-014 (Month 24) - Mean Change from Baseline Intraocular Pressure (mmHg) with Bimatoprost or Timolol at Each Scheduled Visit (ITT with LOCF)

Timepoint	Visit	Bimatoprost QD (N=167)	Timolol BID (N=81)
Hour 0	Baseline	26.4	25.4
	Month 12	-8.6[a]	-5.7
	Month 15	-8.6 [a]	-5.8
	Month 18	-8.4 [a]	-6.0
	Month 21	-8.0 [a]	-5.4
	Month 24	-8.4 [a]	-5.7
Hour 2	Baseline	25.0	23.7
	Month 12	-7.9 [a]	-4.8
	Month 15	-8.0 [a]	-5.1
	Month 18	-8.2 [a]	-5.0
	Month 21	-7.4 [a]	-4.6
	Month 24	-7.8 [a]	-4.6

a Bimatoprost QD vs. timolol $p < 0.001$

Mean H0 IOP values ranged from 17.8 to 18.4 mmHg in the bimatoprost qd group and 19.5 to 20.0 mmHg in the timolol group. For H2, the values ranged from 16.9 to 17.6 mmHg in the bimatoprost qd group and 18.7 to 19.1 mmHg in the timolol group. Bimatoprost qd was statistically superior to timolol at all timepoints and all visits ($p\leq0.006$).

Results of the PP analysis were consistent with the ITT analysis. The "Patient satisfaction" was similar in the 3 treatment groups: 96.3%, 94.6%, and 97.2% in the bimatoprost qd, bid and timolol group, respectively ($p=0.858$). In addition, there was no statistically significant among group difference for the "Pharmacoeconomic evaluation"; at month 24.

Study 192024-014 (36 Months)

Description of the study

From Month 24 patients in the bimatoprost bid-group were in a blinded fashion switched to bimatoprost qd (the group bid/qd). The other two groups continued their treatment regimen unchanged.

Statistical analysis

The primary efficacy variable continued to be mean change from baseline in IOP. In addition the proportion of patients achieving target intraocular pressures at each hour was evaluated. The target levels of ≤13 mmHg up to ≤20 mmHg at 1 mmHg increments were assessed. Furthermore, the proportion of patients who achieved target IOP within the IOP ranges of: ≤15 mmHg, >15 mmHg and ≤18 mmHg, and >18 mmHg was compared between treatment groups. Subject satisfaction questionnaire on a 7-point scale and the Investigator's evaluation of his/her willingness to continue the patient on the current medication (assuming that treatment was still required) and that the medication was commercially available were again assessed. This was called "Pharmacoeconomic evaluation"

Study populations/accountability of patients

A total of 15 of the 23 centres from the 24 months study continued in the 36 months extension. A total of 183 patients were enrolled, with 90 patients continuing in the bimatoprost qd group, 50 patients switching from bimatoprost bid to qd (hereafter called the bimatoprost bid/qd group), and 43 patients continuing with timolol bid. The number of patients who discontinued the study after month 24 and at or before month 36 was 7/90 (7.8%) in the bimatoprost qd group, 8/50 (16.0%) in the bid/qd group and 6/43 (14.0%) of the timolol group. The reason for discontinuation was adverse events for 3 patients in the bimatoprost qd group while no patients in the other groups discontinued for that reason. Discontinuation due to lack of efficacy was reported in 1/90 (1.1%), 3/50 (6.0%), and none, in the bimatoprost qd, bid/qd and timolol groups, respectively.

There were no major differences at baseline in the demography or IOP values. The entry diagnosis was glaucoma for 61.2% and ocular hypertension for 36.6% of the patients. A number of 2.2% had a mixed diagnosis (i.e. one eye with glaucoma and the fellow eye with ocular hypertension).

Efficacy results

Overall at month 36 the mean decreases from baseline in IOP at hours 0 and 2 in patients treated with bimatoprost once daily in the ITT population ranged from 7.1 to 8.3 mmHg. These decreases continued to be statistically significantly greater ($p \leq 0.009$) than those achieved in patients treated with timolol (4.9 to 6.4 mmHg) at every visit. The IOP-lowering effect of bimatoprost bid/qd regimen ranged from 5.8 to 7.8 mmHg. The bimatoprost qd regimen was statistically superior to the bid/qd regimen only at hour 2 on months 27 and 30 and non-inferior at all other timepoints. The bimatoprost bid/qd regimen was statistically superior to timolol at months 27 and 30 ($p \leq 0.048$) and non-inferior at all other timepoints.

Secondary endpoints:

Except at month 36, statistically more patients obtained lower target IOP in the bimatoprost qd than in the timolol group in each interval ≤15, >15 and ≤18, and >18 mmHg ($p<0.049$) at H0 and at all visits at H2 ($p<0.044$).
No statistical significant differences were seen ($p=0.913$) in the patient satisfaction with approximately 95% of all groups being "Slightly to very satisfied" with the anti-glaucoma medication. Furthermore, no major differences between the 3 groups (bimatoprost qd, bimatoprost bid/qd and timolol) were evident in the "Pharmacoeconomic evaluation": 96%, 88% and 92%, respectively were willing to continue treatment ($p=0.24$).

The patients were selected to both studies (24- and 36-month) based on the site's willingness as well as the patients' eligibility and willingness to continue. The CPMP questioned whether bias had been introduced in the selection of centres or patients in their Request for Supplementary Information. The MAH provided 4 analyses to explore the possibility of biases in the selection of patients who continued into the extension phases of the pivotal studies (the reasons given for investigators/sites not proceeding into the extension 24- and 36-month studies, the proportion of patients continuing into the extension phases was similar between the bimatoprost qd group and the timolol group, the mean IOP for patients continuing and for patients not continuing into the second and the third study year and patterns for the most prevalent adverse events in patients entering 24 or 36 months extension which indicate a selection of patients according to adverse events reported). The CPMP concluded that the

analyses provided reassurance and confirmed that no bias had apparently been applied in the selection of investigators/sites or patients proceeding into the extension phases for 24 and 36 months of treatment.

Study 192024-019

Description of the study

Multicentre, investigator-masked, randomised, parallel group 6-month comparative study of the safety and efficacy of once daily application of bimatoprost 0.03% and latanoprost 0.005% in patients with glaucoma or ocular hypertension conducted at 18 sites in the USA.

The criteria of inclusion were patients with ocular hypertension or primary open-angle glaucoma, chronic angle-closure glaucoma with a patent iridotomy, pseudoexfoliative or pigment glaucoma; patients' diagnosis required bilaterally treatment. The IOP at H0 should be ≥22 mmHg but ≤34 mmHg (post-washout), and an asymmetry ≤5 mmHg. For each IOP-lowering-medication a wash-out schedule prior to study entry had been defined. Other adequate precautions against possible interference with study outcome were taken.

Assessments took place pre-study, at baseline, at week 1, and at months 1, 3, and 6. During the trial the IOP was measured at H0, H4 and H8. The primary efficacy variable was mean change from baseline in IOP for recordings at H0, H4 and H8. Secondary parameters were pharmacoeconomic evaluation by the Investigator, the % change from baseline in IOP values, the proportion of patients achieving target levels of ≤15 mmHg, >15 to ≤18 mmHg, and >18 mmHg compared between the two treatment groups. After data lock two separate additional analyses of patients defined as "non responders", i.e. achieving less than 15% and less than 20% decrease in IOP from baseline were included.

Statistical analysis

The study was designed as a non-inferiority trial and ITT analysis with LOCF and PP analyses were performed. A 2-sided 95% confidence interval on the difference in mean IOP change from baseline between the groups was applied. If the upper limit of the confidence interval was less than δ, bimatoprost was considered as non-inferior to latanoprost. Several values for δ were used to calculate the power. There were approximately 135 patients per group in this study providing 91% power to detect a 1.5 mmHg difference.

RESULTS

Study populations/accountability of patients

A total of 269 patients were included, of whom 133 patients were randomised to bimatoprost and 136 patients to latanoprost, constituting the ITT population. The PP population encompassed 259 (96.3%) of the enrolled patients (126:133). The overall frequency of discontinuation by month 6 was 7.4%, with 6.8% and 8.1% in the bimatoprost and latanoprost groups, respectively. The two treatment groups were well balanced in demographic parameters at baseline (sex, race, iris colour, mean deviations in visual field). The mean age was 61.3 years. The distribution of ophthalmic diagnoses was glaucoma (64%) and ocular hypertension (35%) and mixed (2%), i.e. one eye with glaucoma, the other with ocular hypertension.

No significant differences between the two treatment groups were reported in the demography. A wash-out of previous anti-glaucoma medication was required in 68% of the patients in the bimatoprost group, and for 63% in the latanoprost group. In their Request for Supplementary Information the CPMP requested further clarification as to which previous treatment the patients had received.

The responses provided by the MAH showed that the distribution of patients who required wash-out of prostaglandin analogues before entering the study comparing bimatoprost to latanoprost (Study 192024-019) was similar in the two treatment groups, namely 28.6% and 22.1%, respectively. Only one patient was treated with unoprostone prior to study entry, against 67 patients with latanoprost, corresponding to a total of 68 patients (25.3%) of the 269 randomised patients. The explanation for the lack of patients previously treated with bimatoprost being the recent introduction of this compound seemed valid. However, based on these data alone the CPMP considered that the possibility of

inclusion of non-responder patients had not been excluded. In their Follow-On Request for Supplementary Information the CPMP asked the MAH to provide efficacy data excluding patients previously exposed to prostaglandin analogues.

The MAH provided an additional analysis with the comparison of a study sub-population excluding patients, who according to protocol criteria of inclusion required a wash-out period of latanoprost prior to randomisation to the double-blind study period, relative to the total study population. The number of patients in the sub-population treated with bimatoprost was 95 and with latanoprost 107, as opposed to the corresponding distribution in the total study population where 133 patients received bimatoprost and 136 received latanoprost. The results from the sub-population are, as regards to mean baseline IOP-values, the primary end point, i.e. change in IOP from baseline, and minimum and maximum IOP-values, overall very close to what was observed in the total study population. These results are also reflected in the analysis of the proportion of non-responder patients (as defined as a decrease of 20% or less in IOP from baseline).

Though historic information of a possible previous unsuccessful treatment with latanoprost cannot be excluded the CPMP recognised that this likelihood is small.

In conclusion, from the analysis it was evident that the therapeutic results from patients treated with latanoprost just prior to study inclusion, i.e. after the wash-out, are consistent with the results from the overall study population. Hence, although it would have been desirable that the exclusion of latanoprost non-responders was established in the protocol, it is reasonable to conclude that there was no systematic inclusion of latanoprost non-responders.

Efficacy results

Baseline IOP at H0 was 25.0 mmHg and 24.9 mmHg in the bimatoprost and latanoprost groups, respectively. At H4 the IOP values were 24.0 mmHg and 23.3 mmHg for the two groups, respectively, this value was statistically significant different ($p=0.028$). At H8 the values were 22.6 mmHg and 22.5 mmHg for bimatoprost and latanoprost, respectively.

The overall mean decreases from baseline in IOP at all timepoints ranged from 6.0 to 8.2 mmHg for bimatoprost and from 4.9 to 7.2 mmHg for latanoprost. With particular reference to the H0 timepoint, these decreases ranged from 7.6 to 8.2 mmHg for bimatoprost and 6.0 to 7.2 mmHg in the latanoprost group. The mean decrease in IOP was statistically significantly larger in the bimatoprost than the latanoprost group at all measure points at all visits ($p\leq0.025$) in the ITT-analysis.

Due to the statistically significant difference in baseline IOP at H4, an analysis of covariance was also performed for each of the variables. This showed no difference to the conclusions obtained from analyses with no adjustment for difference in baseline. In addition, the mean IOP value was statistically significantly lower in the bimatoprost group than in the latanoprost group at all visits at all hours measured.

The mean percent change from baseline in IOP at H0, H4 and H8 ranged from 26% to 33% in the bimatoprost group and from 21% to 29% in the latanoprost group at week 1, months 1, 3 and 6, respectively. These mean percent changes from baseline in IOP were significantly greater with bimatoprost than with latanoprost at all timepoints and all visits.

Statistically significantly more patients in the bimatoprost group than the latanoprost group achieved an IOP value at all time points at study end in the lower target IOP values in the intervals ≤ 15 mmHg, >15 to ≤ 18 mmHg and >18 mmHg ($p\leq0.026$).

The PP analysis confirmed the ITT results.

The responder rate analysis showed that with bimatoprost 83% to 89% and 69% to 82% of the patients had at Month 6 at the measured time points obtained a ≥15% reduction and a ≥ 20% reduction from baseline, respectively, as opposed to 65% to 72% and 50% to 63% of the patients treated with latanoprost. For both responder rates statistical superiority in favour of bimatoprost was demonstrated. Though not pre-defined this analysis is of some interest as the response rate represents a clinically valuable measurement.

The results substantiate the positive trends observed in the earlier comparative study of 3 months duration, submitted as part of the Response to the CPMP list of Questions to the initial Marketing

Authorisation application and the 1 month comparative study provided in the original Marketing Authorisation application.

Study 192024-013:

Description of the study:

Multicentre, investigator-masked, randomised, parallel group 3 months study where placebo qd (morning) + bimatoprost qd (evening) was compared to Cosopt (dorzolamide 0.2% + timolol 0.05%) bid, in patients with ocular hypertension, primary open angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma or pigment glaucoma and who were uncontrolled on beta-blocker alone after a minimum of 2 weeks therapy. The inclusion criteria required an IOP of ≥22 mmHg and ≤34 mmHg. The primary end point was mean change from baseline IOP. IOP measurements were performed at H0, H2, H8 and H12.

Statistical analysis

Combined non-inferiority and superiority tests for comparison between groups were applied for change from baseline and IOP. If the mean change from baseline IOP with bimatoprost was less than 2 mmHg greater than for Cosopt the power would be 85% with a sample size of 75 per treatment arm. The upper limit of 95% confidence interval was used to claim non-inferiority if the upper limit was ≤2 mmHg.

Results

A total of 177 patients (bimatoprost: 90 and Cosopt: 87) were enrolled of whom 168 patients completed. The mean decrease from baseline in IOP at hour 0 ranged from 6.8 to 7.6 mmHg and was at all visits statistically significantly greater with bimatoprost than with the combination which gave decreases ranging from 4.4 to 5.0 mmHg ($p<0.001$). The mean IOP was statistically lower at the month 3 evaluations at 3 out of 4 timepoints and numerically lower at the fourth point.

Study 192024-015:

Description of the study:

This was an open label, cross-over multicentre study conducted in the USA. The study population was similar to that in the pivotal studies, except that no IOP-limits were defined. During the first 60 days Timoptic XE (0.5% timolol gel) in the morning and Xalatan (latanoprost 0.005%) in the evening were applied. From day 60 to day 120 bimatoprost 0.03% in the evening was applied. Five visits were scheduled.

Statistical analysis

As for efficacy criteria, bimatoprost would be regarded non-inferior to the adjunctive therapy if the mean difference in IOP from day 60 to day 120 was less than 2 mmHg. Bimatoprost was regarded as better than the adjunctive therapy if the upper limit of the 95% confidence interval for the mean change in IOP from day 60 to day 120 was less than zero. A 2-sided 95% confidence interval for the change from baseline, with the paired t-test was applied. A sample size of 75 was demanded.

Results:

A total of 88 patients were enrolled and 74 completed the 120 days study.
The mean H0 IOP value was 18.95 mmHg at baseline. At day 60 (i.e. with timolol+latanoprost treatment) the IOP was 17.85 mmHg, and at day 120 (i.e. with bimatoprost treatment) 18.57 mmHg. At the diurnal points H0, H2, H8 and H12 the upper limits were 0.71 to 1.61 mmHg, i.e. less than 2 mmHg. The bimatoprost treatment was thus regarded as non-inferior to the adjunctive therapy.

These results were obtained in an open, non-randomised study, and the assumptions were less demanding than those usually applied. Numerically, the H0 IOP values at the end of the study period at hours 0, 2, 8 and 12 were higher with bimatoprost than with timolol+latanoprost.

Published literature: Latanoprost non-responder studies

Bimatoprost usage in those primary open-angle or ocular hypertension patients who do not respond to latanoprost was reviewed. A prospective cross-over 15-patient study treated patients with either bimatoprost or latanoprost for 30 days and following a 30-day wash-out the same patients received the other therapy in a masked manner (Gandolfi & Cimino, 2003). Only patients who had previously shown a lack of response to latanoprost (defined as a ≤10% IOP-lowering effect following 6-8 weeks treatment with latanoprost) were included in the study. In order to further evaluate the true effect of each therapy, only one eye of each patient was randomly selected for treatment with the other eye-receiving placebo.

No significant IOP changes from baseline were observed in the untreated eye during each phase of the study. The mean IOP diurnal curve after 30 days on latanoprost did not differ from the untreated baseline. However, the mean IOP readings after 30 days on bimatoprost were significantly lower than the baseline at time points throughout the day. Whilst all of the 15 patients failed to show a >20% decrease from baseline on latanoprost, 13 of the 15 patients did show this degree of decrease from baseline when instilling bimatoprost.

Although, the patient numbers are low, this study does strongly suggest that patients who are latanoprost non-responders have a high probability of responding well to bimatoprost.

A second recently presented study, of 51 patients, supports these findings (Williams, 2003). In the first phase of this study patients were treated with latanoprost in one eye for 8 weeks with IOP evaluations at both weeks 4 and 8. Those patients with an IOP reduction less than or equal to 3 mmHg at both visits, relative to the untreated fellow eye, were considered poor responders to latanoprost and only these patients (n=21; of these 15 were known to be previous latanoprost non-responders) were switched to receive bimatoprost in the same eye that had previously been given latanoprost. On comparing these 21 patients, after 8 weeks of each therapy the mean IOP reduction from baseline with latanoprost was 1.9 mmHg and 5.4 mmHg with bimatoprost for the same patients. Thus the switch to bimatoprost provided a statistically and clinically significant additional mean IOP reduction of 3.5 mmHg.

Due to the low patient numbers, the referenced studies do not allow the drawing of any definitive therapeutic conclusions. However, they would probably justify more comprehensive future clinical trials.

Clinical safety

The clinical development programme for bimatoprost 0.03% ophthalmic solution consisted of 13 phase I to III studies which provided a safety database of 2326 patients with glaucoma or ocular hypertension or normal subjects, including 1708 patients or normal subjects who were exposed to a variety of concentrations and dosing regimen of bimatoprost. Of these 1708 patients, 1219 received a concentration/regimen of bimatoprost alone and 489 bimatoprost in combination with a topical beta-blocker. The remaining 618 patients or normal subjects received active control or vehicle.

Patient exposure

Monotherapy studies (192024-008 and 192024-009)
In the phase 3 monotherapy studies, all 1198 patients who enrolled received at least 1 dose of test medication and are included in the safety analyses: 474 patients instilled bimatoprost 0.03% qd, 483 patients instilled bimatoprost 0.03% bid, and 241 patients instilled timolol 0.5% bid. The mean (range) duration of treatment during the initial 6 months was 171.1 (2 to 228) days in the bimatoprost qd group, 160.2 (1 to 239) days in the bimatoprost bid group, and 174.5 (1 to 216) days in the timolol group.

Adjunctive studies (192024-501 and 192024-502)

In the phase 3 adjunctive studies, all 722 patients who enrolled received at least 1 dose of test medication and are included in the safety analyses: 246 patients instilled bimatoprost 0.03% qd, 243 patients instilled bimatoprost 0.03% bid, 138 patients instilled latanoprost 0.005% qd, and 95 patients instilled vehicle bid, each adjunctively with a topical beta-blocker bid. The mean (range) duration of treatment during the 3 months was 80.5 (1 to 116 days) in the bimatoprost qd/beta-blocker group, 78.4 (1 to 120 days) in the bimatoprost bid/beta-blocker group, 82.4 (1 to 109 days) in the latanoprost/beta-blocker group, and 83.8 (1 to 159 days) in the vehicle/beta-blocker group. Overall, 90.9% (656/722) of patients completed 3 months treatment.

Studies in healthy subjects and dose finding studies

A total of 108 healthy, normal subjects (including 23 elderly subjects over 65 years in study 012) participated in the pharmacokinetic and mechanism of action studies. The 4 dose-ranging studies were conducted in 154 patients with open-angle glaucoma or ocular hypertension (studies 192042-001, 192042-002, 192042-003 and 192042-004). The duration of treatment was 28 days in studies 002, 003, and 004.

Adverse events and serious adverse events/deaths

Studies in healthy subjects and dose finding studies

There were no deaths, other serious AEs, or other significant AEs in the studies in healthy subjects.

In the dose finding study 001, the most frequently reported treatment-related AEs across all bimatoprost groups were conjunctival hyperaemia, headache, dry eye, gastrointestinal symptoms (diarrhoea, nausea, and abdominal pain), and eye ache/pain. No serious AEs were reported during the study, and no patient discontinued due to an AE.

In study 002, the most frequently reported AEs across all bimatoprost groups were conjunctival hyperaemia, dry eye, and diarrhoea. The only statistically significant among-group difference was for overall AEs, with significantly higher incidences with bimatoprost 0.01% and 0.03% than with vehicle ($p=0.003$). There were no study discontinuations due to AEs. Conjunctival hyperaemia was observed on gross inspection in all treatment groups. The mean increases were significantly greater with bimatoprost treatment than with timolol at most follow-up visits, and greater than with vehicle at some visits. The maximum hyperaemia grade for the active bimatoprost groups increased to "severe" during bid dosing. Conjunctival hyperaemia was the only significant ocular finding.

In study 003, the only AE with a statistically significant difference in incidence between bimatoprost and vehicle was the most frequently reported AE, conjunctival hyperaemia ($p=0.043$). Other ocular events reported for more than 1 patient were burning sensation in the eye, blepharitis, and visual disturbance in the bimatoprost group, and blepharitis and eye discharge in the vehicle group. Non-ocular AEs were reported in 3 patients in the bimatoprost group. There were no serious AEs. Two patients discontinued treatment due to AEs. There were statistically significant increases in the severity of bulbar hyperaemia by gross inspection and conjunctival hyperaemia by biomicroscopy during treatment with bimatoprost ($p\leq0.030$). The increased severity was generally greater with bimatoprost than with vehicle ($p\leq0.025$). An increase of at least 1 severity grade from baseline conjunctival erythema by biomicroscopy was reported for all 16 patients (100%) in the bimatoprost group and 3 patients (18.8%) in the vehicle group ($p<0.001$).

In study 004, the most frequently reported treatment-related AEs in the bimatoprost groups were conjunctival hyperaemia and ocular pruritus. No serious AEs were reported during the study and four patients discontinued the study due to AEs.

Monotherapy Studies

Treatment-related AEs included those events rated by the investigator as possibly, probably, or definitely related to study medication. During the first 6 months of the phase 3 monotherapy studies, 1 or more treatment-related AEs were reported by 76.2% (361/474) of patients treated with bimatoprost qd, 88.8% (429/483) of patients treated with bimatoprost bid, and 41.9% (101/241) of patients treated with timolol. The overall incidence of treatment-related AEs was statistically significantly lower in patients treated with timolol than in patients treated with either regimen of bimatoprost ($p<0.001$), and

was statistically significantly lower in patients treated with bimatoprost qd than in patients treated with bimatoprost bid ($p<0.001$). In patients using bimatoprost qd compared to those using timolol, there was a statistically significantly higher incidence of conjunctival hyperaemia, growth of eyelashes and eye pruritus (all $p<0.001$), eye dryness ($p=0.008$), blepharal pigmentation ($p=0.002$), erythema eyelid ($p=0.011$) and eyelash discoloration ($p=0.020$). In patients using bimatoprost bid compared to those using timolol, there was a statistically significantly higher incidence of conjunctival hyperaemia, growth of eyelashes, eye pruritus, eye dryness, blepharal pigmentation, foreign body sensation, eyelash discoloration and photophobia (all $p<0.001$), eye pain ($p=0.003$), erythema eyelid ($p=0.020$), and eyelid pruritus ($p=0.007$). In patients using bimatoprost bid compared to bimatoprost qd, there was a statistically significantly higher incidence of conjunctival hyperaemia, growth of eyelashes, photophobia and eyelid pruritus (all $p<0.001$), blepharal pigmentation ($p=0.003$), eye pain ($p=0.009$), and foreign body sensation ($p=0.015$). The majority of treatment-related AEs were mild to moderate in severity. Incidences and types of non-ocular treatment-related AEs were similar among the 3 pooled treatment groups and there were no statistically significant differences among the treatment groups for these events. The only non-ocular treatment related AEs occurring at an incidence of ≥1% in the bimatoprost qd group were headache, asthenia and 'liver function tests abnormal'. Of the 5 occurrences of abnormal liver function tests in the bimatoprost qd group, 2 were moderate, 3 were mild, and all were considered possibly related to study medication. All cases of liver dysfunction are explainable by other eliciting factors like other disease, alcohol or medication use. One patient was reported with elevated γ-glutamyl transpeptidase (GGT) at baseline and throughout the study. No patient discontinued due to laboratory findings.

Discontinuation due to adverse events in Phase 3 Monotherapy studies:

Overall 7.0% (33/474) of patients receiving bimatoprost qd, 12.6% (61/483) of patients receiving bimatoprost bid, and 3.3% (8/241) of patients receiving timolol discontinued due to AEs ($p<0.001$). Significantly larger percentages of patients discontinued due to AEs in the bimatoprost bid group than in either the bimatoprost qd or timolol groups, and in bimatoprost qd group than in the timolol group ($p\leq0.048$).

The most common AE leading to discontinuation was conjunctival hyperaemia which led to discontinuation in 3.4% (16/474) of patients receiving bimatoprost qd, 5.2% (25/483) of patients receiving bimatoprost bid, and 0.4% (1/241) of patients receiving timolol ($p=0.005$). Conjunctival hyperaemia and growth of eyelashes were the only AEs for which there was a statistically significant difference between the groups in the incidence of patients discontinuing the studies. A higher percentage of patients treated with either bimatoprost qd or bid discontinued due to conjunctival hyperaemia than those treated with timolol ($p\leq0.014$) and a higher percentage of patients discontinued due to growth of eyelashes in the bimatoprost bid group (1.2% 6/483) than in the qd group (0%, 0/474, $p=0.031$).

Other AEs leading to discontinuation occurring at an incidence of 2 or more patients (0.4% in the bimatoprost groups) were *in the bimatoprost qd group*: Eye pruritus, (8 patients, 1.7%), eye irritation, (4 patients, 0.8%), eye dryness, (3 patients, 0.6%), allergic conjunctivitis, blepharal pigmentation, eye pain, foreign body sensation, burning sensation in eye (2 patients each, 0.4*%). In the bimatoprost bid group*: Eye pruritus, blepharal pigmentation, eye pain, (8 patients each, 1.7%); growth of eyelashes, photophobia (6 patients each, 1.2%); foreign body sensation (4 patients, 0.8%), eye dryness, allergic conjunctivitis (3 patients each, 0.6%); eye irritation, burning sensation in eye, asthenia, epiphora, eyelid oedema, iritis, diarrhoea, keratitis, optic nerve (NOS) (disc haemorrhage), visual disturbance (2 patients each, 0.4%). *In the timolol group*: No AEs leading to discontinuation occurred at an incidence of 2 or more patients. AEs leading to discontinuation occurring at single patient incidence (0.4%) were; conjunctival hyperaemia, eye irritation, foreign body sensation, conjunctival oedema, chest pain, dypsnea, visual field defect, accidental injury, infection, and respiratory disorder.

Serious Adverse Events in Phase 3 Monotherapy Studies:

Serious adverse events (SAEs) were reported for 4.9% (23/474) of patients treated with bimatoprost, 4.1% (20/483) of patients treated with bimatoprost bid, and 4.1% (10/241) of patients treated with timolol ($p=0.844$ for among-group comparison). Except for 1 case in the timolol group, all SAEs were non-ocular. Only 3 of the SAEs were considered to be possibly related to the study medication: in the

timolol group 1 patient had corneal oedema and a second patient was hospitalised due to acute pulmonary distress; in the bimatoprost qd group, 1 patient was hospitalised for chest pain and a diagnosis of coronary artery disease was made. The patient had a history of systemic hypertension. Treatment was continued for 2 months beyond the event although the investigator had considered it possibly related to treatment. There was 1 death due to a myocardial infarction. The patient, a 73 year old male with a history of diabetes, hypertension, and daily tobacco use, had been receiving bimatoprost qd and the event was considered unrelated to study treatment.

Phase 3 Adjunctive Studies

Treatment-related AEs included those events rated by the investigator as possibly, probably, or definitely related to study medication. During the 3 months of the phase 3 adjunctive studies, 1 or more treatment-related AEs were reported by 56.1% (138/246) of patients treated with bimatoprost qd/beta-blocker, 72.4% (176/243) of patients treated with bimatoprost bid /beta-blocker, 34.8% (48/138) of patients treated with latanoprost/beta-blocker and 27.4% (26/95) of patients treated with vehicle/beta-blocker. Overall incidences of treatment-related AEs were statistically significantly lower in patients treated with latanoprost/beta-blocker than in patients treated with either regimen of bimatoprost/beta-blocker ($p<0.001$) and were statistically significantly lower in patients treated with vehicle/beta-blocker than in patients treated with either regimen of bimatoprost/beta-blocker ($p<0.001$). Overall incidences of treatment-related AEs were also statistically significantly lower in patients treated with bimatoprost qd/beta-blocker than in patients treated with bimatoprost bid/beta-blocker ($p<0.0019$).

In patients using bimatoprost qd/beta-blocker compared to latanoprost/beta-blocker, there was a statistically significantly higher incidence of conjunctival hyperaemia ($p=0.004$) and growth of eyelashes ($p=0.001$). In patients using bimatoprost bid/beta-blocker compared to latanoprost/beta-blocker, there was a statistically significantly higher incidence of conjunctival hyperaemia and growth of eyelashes (both $p<0.001$), eye pruritus ($p=0.004$), blepharal pigmentation ($p=0.011$) and eye pain ($p=0.004$). In patients using bimatoprost bid/beta-blocker compared to bimatoprost qd/beta-blocker, there was a statistically significantly higher incidence of conjunctival hyperaemia ($p<0.001$), growth of eyelashes ($p=0.015$), eye pruritus ($p=0.002$), blepharal pigmentation ($p=0.042$) and eye pain ($p=0.011$). In patients using bimatoprost qd/beta-blocker compared to vehicle/beta-blocker, there was a statistically significantly higher incidence of conjunctival hyperaemia and growth of eyelashes (both $p<0.001$). In patients using bimatoprost bid/beta-blocker compared to vehicle/beta-blocker, there was a statistically significantly higher incidence of conjunctival hyperaemia and growth of eyelashes (both $p<0.001$), eye pruritus ($p=0.006$), blepharal pigmentation ($p=0.008$) and eye pain ($p=0.023$). The majority of treatment-related AEs were mild to moderate in severity. The only non-ocular treatment-related AE occurring at an incidence of ≥1% in either bimatoprost/beta-blocker group was headache. Incidences and types of non-ocular treatment-related AEs were similar among the 2 pooled bimatoprost/ beta-blocker groups, the latanoprost group and the vehicle group. There were no statistically significant among-group differences for non-ocular treatment-related AEs.

In adjunctive study 192024-501, treatment-related iritis was reported for 1 patient in the bimatoprost qd/beta-blocker group and 2 patients in the bimatoprost bid/beta-blocker group. In study 192024-502 there were no reports of treatment-related iritis or uveitis. No cases of cystoid macular oedema were reported in either of the 2 adjunctive studies. Only 1 patient discontinued due to treatment-related iritis/uveitis.

Discontinuations Due to Adverse Events in Phase 3 Adjunctive Studies

Overall 4.1% (10/246) of patients receiving bimatoprost qd/beta-blocker, 9.1% (22/243) of patients receiving bimatoprost bid/beta-blocker, 1.4% (2/138) of patients receiving latanoprost/beta-blocker, and 1.1% (1/95) of patients receiving vehicle/beta-blocker discontinued the study due to AEs ($p=0.001$). Significantly larger percentages of patients discontinued due to AEs in the bimatoprost bid/beta-blocker group than in either the bimatoprost qd/beta-blocker group ($p=0.026$), the latanoprost/beta-blocker group ($p=0.003$) or the vehicle/beta-blocker group ($p=0.009$). There was no statistically significant difference between the percentage of patients discontinuing the study in the bimatoprost qd/beta-blocker group and the percentages of patients discontinuing in either the

latanoprost/beta-blocker group or the vehicle/beta-blocker group. The most common AE leading to discontinuation was conjunctival hyperaemia. There were no discontinuations due to conjunctival hyperaemia in either the latanoprost/beta-blocker or vehicle/beta-blocker groups.

Serious Adverse Events in Phase 3 Adjunctive Studies

Serious adverse events (SAEs) were reported for 2.4% (6/246) of patients treated with bimatoprost qd/beta-blocker, 1.6% (4/243) of patients treated with bimatoprost bid/beta-blocker, 0.7% (1/138) of patients treated with latanoprost/beta-blocker and 1.1% (1/95) of patients treated with vehicle/ beta-blocker (p=0.718 for among-group comparison). Only 1 of the SAEs was considered to be possibly related to the study medication. There were no deaths during study 501 or the first 3 months of study 502.

Laboratory findings

Methods of evaluation of ophthalmological safety parameters: Visual acuity (measured with a standard Early Treatment Diabetic retinopathy Study (ETDRS) chart, and recorded in Snellen equivalent units and translated into lines), and slit lamp biomicroscopy was performed prestudy and at each follow-up visit included evaluations of lid (erythema/hyperaemia. oedema and other findings incl. lashes), conjunctiva (bulbar and palpebral for erythema/hyperaemia and oedema), cornea (oedema, staining/erosion, endothelial pigment and endothelial dystrophy), anterior chamber (cells, flare, anterior and posterior synecchiae), lens (cataract), iris pathology, vitreous pathology each graded as none=0, trace=0.5, mild =1, moderate=2 or severe=3. Ophthalmoscopy (prestudy and at month 6 or 3, according to the duration of the study), with fundus pathology (same grading scale) and cup/disc ratio on the Allergan Armaly chart on a scale from 0-0.9 with the 6 or 3 months value compared to baseline, and visual field examination. Visual field was evaluated using a Humphrey 24-2 full threshold automated perimetry test. At selected centres laser flaremeter and endothel cell density investigations were in addition performed. Iris colour, corneal pachymetry, heart rate and blood pressure also were evaluated.

Visual acuity

The majority, namely 87-95%, did not show any change in visual acuity during the 6 months monotherapy and 3 months adjunctive studies. For the rest, there was no statistical significant differences in the frequency of patients who had a decrease of 2 lines or more (p=0.801/0.887/0.100/0.126 for each of the trials).

Ophthalmoscopy and slit lamp biomicroscopy

Monotherapy studies: An increase in conjunctival or erythema hyperaemia from baseline was noted in approximately 38% in the bimatoprost qd group, 47% in the bid group, and approximately 7% in the timolol group (p<0.001). Also an increase in the lid erythema (~ 6% in the qd group and ~ 8% in the bid group) was statistically more frequent in the bimatoprost groups than in the timolol group (0-1%). Increases of at least grade 1 in the severity of anterior chamber cells or flare resulted in the discontinuation because of iritis in 3 cases, and because of uveitis in 2 cases, all after approximately 2 weeks of treatment with bimatoprost qd or bid Further 3 patients in the bimatoprost groups had either mild flare, or 1-5 or 6-25 cells in the anterior chamber at isolated visits, and a single patient in the timolol group had 1-5 cells and trace flare at one visit.

Growth of eyelashes was reported statistically significantly more frequent in the bimatoprost qd and bid, groups than in the timolol treated group, namely in approximately 22%, 32%, and 5%, respectively.
Adjunctive beta-blocker studies: Increase in conjunctival hyperaemia was distributed with 15%, 27%, and 11% in bimatoprost qd, bid, and latanoprost treated patients, respectively (p<0.001), however, the difference between bimatoprost qd and latanoprost was not statistically significant. Also for the growth of eyelashes a statistically significant difference was observed: 19%, 25%, and 9% in the three groups, respectively. Trace levels of anterior chamber cells and/or flare were reported in 7 patients, of which 3 were noteworthy as the findings were persistent, and in one case the patient was withdrawn because of uveitis; these 3 cases occurred in the bimatoprost groups.

Laser flaremeter analysis was performed at selected centres in a subset of 123 and 187 patients in study 192024-008 and –009, respectively. No statistical significant differences across the 3 treatment groups were observed.

Endothelial cell count was carried out at selected centres in 126 and 215 patients in study –008 and -009, respectively. No statistically significant differences across the treatment groups were reported.

Cup/disc ratio

In the monotherapy studies the majority (79% and 72% in study 008 and 009, respectively) had no change from baseline to the end of the 6 months period. No specific pattern between the treatment groups in the smaller part of patients who exhibited a worsening during the study period was obvious. In the adjunctive studies, around 90% had no change from baseline. In study 501, a numeric difference in the number of patients with a worsening was found in the bimatoprost groups, where 2/146, resp. 2/138 (1.4%) of the qd, respectively, bid group versus 0 patients in the latanoprost group. A similar frequency in the bimatoprost groups versus 1% in the vehicle group was reported from study 502.

Visual field

No statistically significant differences in the changes in visual field were disclosed in the monotherapy or adjunctive studies. The vast majority, around 95% in the monotherapy studies and around 92% in the adjunctive studies, showed less than 5 dB change from baseline, and no statistical significant differences across the treatment groups in this respect were identified.

Other:
Iris colour: Increased iris pigmentation was reported in 1% of the bimatoprost treated patients in the 6 months monotherapy studies, and in the 3 months beta-blocker adjunctive studies in 2-3% in the bimatoprost treated groups, with no cases in the latanoprost and vehicle treated patients. No specific iris colour group was dominating with this adverse event.

Both in the monotherapy and the adjunctive studies the changes in heart rate and blood pressure in patients treated with bimatoprost were generally small and were not considered clinically relevant.

Discussion on clinical safety

Near 7% of patients discontinued the phase 3 studies due to any AE with once daily administration. In every comparison (both as monotherapy and as adjunctive therapy) the finally proposed dosage regimen of 0.03% once a day (qd) proved better tolerated than the alternative dosage (0.03% twice a day –bid-). This supports the proposed dosage, initially selected on the basis of the higher effect of the bid regimen. A number of adverse events not previously seen in the earlier phase studies became apparent during the phase III studies, including growth of eyelashes, blepharal pigmentation and iridial pigmentation.

Bimatoprost seems to be worse tolerated than timolol and perhaps also than latanoprost. The overall incidence of treatment-related AEs was statistically significantly lower in patients treated with timolol than in patients treated with either regimen of bimatoprost in monotherapy studies. Similarly, incidences of treatment-related AEs were statistically significantly lower in patients treated with latanoprost/beta-blocker than in patients treated with either regimen of bimatoprost/beta-blocker and were statistically significantly lower in patients treated with vehicle/beta-blocker than in patients treated with either regimen of bimatoprost/beta-blocker.

Non-ocular, treatment related adverse events occurring at an incidence of ≥1% in the bimatoprost qd group included headache, asthenia and liver function tests abnormalities.
The most frequently reported ocular, bimatoprost treatment-related AEs were conjunctival hyperaemia, eyelash growth and ocular pruritus. Conjunctival hyperaemia was responsible for 3.4% and 1.2% of discontinuations in the monotherapy and adjunctive studies respectively. This is a similar pattern to that of the only $PGF_{2\alpha}$ analogue antiglaucoma agent currently on the market (latanoprost) but the frequency with bimatoprost appears higher. The other active comparator included in the phase 3 trials, timolol induced, as expected, considerably less treatment-related AEs.

When the less frequent (less than 1%) reactions are considered, the trend seems to be the same (higher frequency with bimatoprost than with timolol and perhaps also than with latanoprost) although the

small numbers make the analysis less conclusive (e.g. iritis and uveitis were seen with bimatoprost monotherapy but not with timolol). In the monotherapy studies intraocular inflammation was reported as treatment-related iritis for 0.4% (2/474) of patients treated with bimatoprost qd and 1.0% (5/483) of patients treated with bimatoprost bid, and as treatment-related uveitis for 0.2% (1/474) of patients with bimatoprost qd and 0.2% (1/483) of patients with bimatoprost bid. In the adjunctive studies there were 3 occurrences of iritis/uveitis in patients treated with bimatoprost-bid/beta-blocker (1.2%) and 1 occurrence in patients treated with bimatoprost qd/beta-blocker (0.4%). There were no such occurrences in patients treated with latanoprost/beta-blocker or vehicle/beta-blocker. This suggests that few patients prone to develop iritis/uveitis might have been included in the trial (published data with latanoprost report an anterior uveitis incidence of 6.4%) and that the obtained iritis/uveitis figures might have been higher in other populations. There were no reports of cystoid macular oedema associated with qd or bid dosing in either the monotherapy or adjunctive phase 3 clinical trials.

No specific interaction studies have been submitted even if during the phase 3 monotherapy studies, over 87% of patients were receiving concomitant medications during the initial 6 months of treatment and in the adjunctive studies, study medication was administered adjunctively with a beta-blocker for 3 months. There were no AEs reported suggestive of a drug-drug interaction between bimatoprost and any systemic medication.

In elderly patients, the safety profile of bimatoprost was similar and with few notable differences in types and incidences of AEs. There was no apparent different safety profile when the data were analysed by sex, race or iris colour.

Clinical safety first line therapy

Study 192024-014 (24 months):

The mean duration of exposure was similar among the three treatment groups being 687 days for bimatoprost qd, 664 days for bimatoprost bid and 702 days for timolol.

One or more treatment related adverse events were reported for 42.5%, 45.0%, and 21.0% of patients in the bimatoprost qd, bid, and timolol groups, respectively ($p<0.001$). A statistically significant higher frequency of conjunctival hyperaemia, growth of eye lashes and superficial punctate keratitis (in the bid group only) was reported for the bimatoprost groups than for the timolol group. The majority of adverse events were mild.

Adverse events led to discontinuation in 16 of 379 patients prior to month 24, with the distribution of 5/167 (3.0%) in the bimatoprost qd treatment group, 7/131 (5.3%) in the bimatoprost bid group, and 4/81 (4.9%) in the timolol group. Apart from 2 patients with allergic conjunctivitis, one patient with conjunctival hyperaemia, one with choroidal folds OD, all in the bid group, and one patient with dyspnoea in the timolol group, these adverse events were not regarded as treatment related.

Serious adverse events in this study were recorded for 15/167 (9.0%) of patients in the bimatoprost qd group, for 14/131 (10.7%) in the bimatoprost bid group, and for 9/81 (11.1%) in the timolol group. These differences were not statistically significant ($p=0.836$), and none were regarded as related to the study medication.

One or more adverse events were reported for 128/167 (76.6 %) of the bimatoprost qd group, for 104/131 (79.4 %) of the bimatoprost bid group, and for 55/81 (67.9 %) of the timolol group. These figures do no differ statistically ($p=0.160$).

The treatment-related adverse events reported, are shown in the table below.

Number (%) of Patients with Treatment related, reported by ≥ 3.0% in Either Bimatoprost Treatment Group

BODY SYSTEM Preferred Term	Bimatoprost QD (N = 167)	Bimatoprost BID (N = 131)	Timolol (N = 81)	Among-group P-value[a]
SPECIAL SENSES (OCULAR)				
conjunctival hyperaemia	22 (13.2%)	21 (16.0%)	0 (0.0%)	< 0.001
growth of eyelashes	11 (6.6%)	8 (6.1%)	0 (0.0%)	0.037
eye pruritus	5 (3.0%)	1 (0.8%)	0 (0.0%)	0.193
superficial punctate keratitis	1 (0.6%)	6 (4.6%)	0 (0.0%)	0.029

a Among-group p-value based on Fisher's exact test.

A visual acuity deterioration of 2 or more lines from Day 0 baseline was reported for 18.0%, 17.6%, and 11.1% in the bimatoprost qd, bid and the timolol group, respectively. However, for the majority of patients, namely 81.3%, no change in VA was reported. Major differences among the three groups were not found for the evaluation of ophthalmoscopy, cup/disc ratio and visual fields.

The biomicroscopy examination revealed at least a 1-grade increase of severity from baseline for conjunctival hyperaemia in 43.1%, 49.6%, and 8.6% of patients in the bimatoprost qd, bid and timolol groups, respectively. This was a statistically greater percentage of patients in the bimatoprost groups compared with timolol. Eyelash growth; lid blepharitis, and lid erythema were also more frequently reported in the bimatoprost groups.

One case of cystoid macular oedema, not considered treatment related, was reported in the bimatoprost qd group and 2 treatment-related severe cases, namely vitreous haemorrhage and visual disturbance, were noted in the bimatoprost qd group.

No cases of intraocular inflammation or increased iris pigment were reported.

Changes in laboratory parameters were unremarkable.

Study 192024-014 (36 months):

The mean duration of exposure was similar for the three groups and ranged between 744 and 1168 days, with 1086 days, 1072 days and 1078 days for the bimatoprost qd, bid, and timolol groups, respectively. For 82.5% of the study population the treatment duration was 36 months.

One or more treatment related adverse events were reported in 28.9%, 34.0% and 25.6% of patients in the bimatoprost qd, bid/qd and timolol groups, respectively (p=0.674). Statistically significantly more patients had conjunctival hyperaemia in the bimatoprost qd and bid/qd groups than in the timolol group. The majority of treatment related adverse events were rated as mild.

Three patients in the bimatoprost qd group and none in the two other groups were withdrawn because of adverse events. These adverse events were not regarded as treatment related.

The frequency of adverse events was 73/90 (81.1%), 42/50 (84 %) and 32/43 (74.4 %) in the three groups, bimatoprost bid/qd, and timolol treatment groups, respectively (p=0.512).

The most commonly reported adverse event was again conjunctival hyperaemia, reported in 13.3% in the bimatoprost qd, 18% in the bimatoprost bid/qd, and 0% in the timolol group (p≤0.009).

Treatment related adverse events, are shown in the table below.

Number (%) of Patients with Treatment related Adverse Events, Reported by ≥ 3.0% in Any Treatment Group

BODY SYSTEM Preferred Term	Bimatoprost QD (N = 90)	Bimatoprost BID/QD (N = 50)	Timolol (N = 43)	Among-group P-value[a]
SPECIAL SENSES (OCULAR)				
conjunctival hyperaemia	11 (12.2%)	7 (14.0%)	0 (0.0%)	0.018
foreign body sensation	3 (3.3%)	1 (2.0%)	0 (0.0%)	0.810
superficial punctate keratitis	2 (2.2%)	3 (6.0%)	0 (0.0%)	0.239
growth of eyelashes	2 (2.2%)	2 (4.0%)	0 (0.0%)	0.568
visual disturbance	1 (1.1%)	0 (0.0%)	2 (4.7%)	0.210
eye dryness	0 (0.0%)	3 (6.0%)	1 (2.3%)	0.040
eye pruritus	0 (0.0%)	2 (4.0%)	1 (2.3%)	0.129
cataract (nos)	0 (0.0%)	0 (0.0%)	2 (4.7%)	0.054

a Among-group p-value based on Fisher's exact test.

Serious adverse events were reported for 8/90 (9%), 5/50 (10%) and 6/43 (14%) in the bimatoprost qd, bimatoprost bid/qd and timolol group, respectively. The investigators did not judge any of these adverse events to be treatment related.

A visual acuity deterioration of 2 or more lines from Day 0 baseline was reported for 21.1%, 26.5%, and 18.6% in the bimatoprost qd, bid/qd and the timolol group, respectively. However, for the majority of patients no change in VA was reported. The cup/disc ratio was unchanged for the majority of patients, but for 8/89 (9%) in the qd group a worsening was noted; this is opposed to 2% and 0% in the bid/qd and timolol group, respectively. However, this worsening was not reflected in a deterioration of the visual field in these 8 patients. No statistical significant differences in change in mean deviation for visual field was observed (p=0.186).

On biomicroscopy, an increase of at least one grade in severity from baseline was reported for conjunctival hyperaemia in 50.0%, 46.0% and 9.3% of patients in the bimatoprost qd, bimatoprost bid/qd and timolol groups, respectively (p<0.001). For the majority of patients it was graded as trace to moderate and the mean score was between trace and mild for both bimatoprost groups at each follow-up visit.

Laboratory measurements were unremarkable.

No cases of intraocular inflammation or increase in iris pigmentation were recorded up to the 36 months time point.

In the 12-24 months study the rate of completion of study period was 78%, 67%, and 81% in the bimatoprost qd, bimatoprost bid and timolol groups, respectively. In the 24-36 months study the corresponding figures were 92%, 84% (bimatoprost bid/qd), and 86%, respectively. Thus a decrease in tolerability towards bimatoprost is not indicated.

Study 192024-019:

Treatment-related adverse events were reported in 83/133 (62.4%) and 45/136 (33.1%) in the two groups (p<0.001), respectively. Conjunctival hyperaemia, growth of eyelashes and eye pruritus were all statistically significantly higher with bimatoprost than with latanoprost. A total of 11 patients discontinued because of adverse events: 6/133 (4.5%) in the bimatoprost and 5/136 (3.7%) in the latanoprost group. This difference was not statistically significant (p=0.768). The leading cause in the bimatoprost group was conjunctival hyperaemia with 3/133 patients (2.3%).

Serious adverse events were reported for 3.0% and 5.9%, in the bimatoprost and latanoprost groups, respectively (p=0.377). None were judged to be treatment related.

The visual acuity remained unchanged during the study for the majority of the patients in both groups, i.e. for 93.1% and 91.9%, in the bimatoprost and latanoprost groups, respectively. A statistically, but presumably not clinical relevant difference in favour of latanoprost (0.2 versus 0.4 in line number) was noted for the VA mean change. The cup/disc ratio was unchanged for approximately 98% of the patients in both groups.

Parameters related to progression of glaucoma, i.e. cup/disc ratio, visual field and ophthalmoscopy, were unremarkable for both groups in this study. This is consistent with the usually rather slow progression of these signs.

Slit lamp biomicroscopy revealed a significant higher frequency of findings reported for the bimatoprost than for the latanoprost group: 48.9% versus 22.1% (p<0.001). This was dominated by the difference in the incidence of increase from baseline in severity of conjunctival erythema/hyperaemia: 39.1% versus 14.7% (p<0.001). However, the mean grades of hyperaemia were low for both groups being 0.55 and 0.28 (on the 0-3 scale) in the bimatoprost and latanoprost groups, respectively (p<0.001) at month 1.

One case of iritis was reported in the latanoprost group, no cases of ocular inflammation were recorded in the bimatoprost group. Cases of cystoid macular oedema were not reported in either group. Because of technical issues 38% of the photographs taken to evaluate changes in iris pigmentation were unevaluable, and the analysis was therefore not done. One case of increase in iris pigmentation was noted clinically in the bimatoprost group at 6 months, and none in the latanoprost group.

The CPMP requested the MAH to provide in tabulated form the adverse events related to the exposure occurred during the bimatoprost/latanoprost comparison study, as well as the rates and reasons for discontinuation in both the latanoprost and bimatoprost group.

The MAH provided a review of the most prevalent adverse events with particular attention to the mean time to onset, discontinuations rates and reasons for discontinuation. The CPMP concluded that the rate of discontinuation was low and no particular pattern of reasons for withdrawal is evident in any of the groups. The incidence of conjunctival hyperaemia is, in keeping with previous information, higher with bimatoprost than with latanoprost.

Studies contributing supportive data, 192024-013 and 192024–015:

In study 192024-013 more patients in the Cosopt than in the bimatoprost group, namely 49.4% versus 44.4% (p=0.507) reported treatment-related adverse events. Hyperaemia was recorded in 34.4% patients in the bimatoprost group as opposed to 17.2% of the patients in the Cosopt group (p=0.009). Three patients in each group discontinued because of ocular adverse events. Three serious adverse events, which were considered not treatment related, were reported in the bimatoprost group.

In study 192024-015 no statistically significant differences in the overall incidence of reported adverse event were noted for the two treatment periods. Treatment related adverse events were recorded for 20.5% and 21.6% of the bimatoprost and timolol+latanoprost period, respectively. There were no reports of intraocular inflammation, iris pigmentation or cystoid macular oedema.

Safety in special populations

Since bimatoprost has been in the marketplace, occasional questions have arisen from prescribers relating to the labelled undesirable effect of elevated liver function tests. Focusing on the pertinent liver function tests, the original review of the overall clinical trial 12-month data showed that the vast majority of patients had baseline values between the lower limit of normal and twice the upper limit of normal. These values remained relatively unchanged in all treatment groups in this time-period. Where there appeared to be clinically relevant worsening, it was possible to document a medical history or a concomitant medication, which could at least possibly explain the abnormality. However, to address the question further, a full review of patients with hepatic dysfunction was performed.

Patients with hepatic dysfunction were studied. They included those with a history of mild liver disease at time of start of the Phase III development programme and/or those patients with one or more abnormal liver function tests at baseline (defined as 1.5 times the upper limit of normal range for relevant parameters). All patients who were randomised to study medication were followed. In addition, those who then participated in the extension study, both Months 24 and 36, was described. A total of 41 patients enrolled with a pre-existing history of liver function disease and/or abnormal liver function tests at baseline. Of these, 18 received bimatoprost QD, 12 received bimatoprost BID and 11 patients were randomised to the timolol arm. Of these 8, 2 and 2 patients, respectively, enrolled into the Month 24 extension. Over the course of the two years none of the 41 patients discontinued the study due to changes in liver function.

In addition, although it is understood that ophthalmologists will not be routinely assessing liver function, there have been no spontaneous reports of elevated liver function from the post-marketing area.

In summary, although the numbers are relatively small, it can be concluded that patients with prior hepatic dysfunction are not at increased risk of worsening of established disease. However in their Request for Supplementary Information the CPMP requested submission of hepatic safety tabular data describing the incidence of changes from baseline and the magnitude of such changes in all patients, not only from those with baseline hepatic impairment.

The MAH in its responses reviewed all normal to high shifts in the patients' liver function parameters, ALT, AST and bilirubin. Occurrences of repeated high values were also analysed. The vast majority represented shifts to up to 1.5 times the upper limit of value, with a few cases of values above 2.5 times the upper limit of normal value. These cases were evenly distributed across the three treatment groups, bimatoprost qd, bid, and timolol groups.

Isolated cases have been reported in all treatment groups. The frequency is similar in the two bimatoprost dosing regimen groups, which is reassuring. Moreover, a worsening in the hepatic function parameters during the 3-year study period was not noted.

Post-marketing surveillance

The first Lumigan Periodic Safety Update Report covering the period from European launch in March 2002 till September 2002 was reviewed by the CPMP and overall it was concluded that the safety profile did not raise any signals of concern and recommended that the SPC should remain unchanged.

A further review of the post marketing experience from September 2002 until February 15, 2003 reports was performed specifically for this submission. Only two unexpected serious events have been received. These were of a seizure with no other reports of seizure received in that time-period. The second case was of a tear in the posterior capsule with associated ocular pain, blurred vision and nausea. In both cases the relationship to bimatoprost was unknown. Review of the suspected treatment-related non-serious adverse events reveals no obvious pattern.

Specific adverse events (iris pigmentation, eyelash growth, conjunctival hyperaemia and cystoid macula oedema)

The adverse events of particular interest namely iritis, uveitis, cystoid macular oedema and iridial pigmentation were not reported in the time period from month 12 to month 36 in study 192024-014. Just under 100 patients have been followed for a full 3 years.

There were only 2.2% new cases of eyelash growth reported in the time period between month 24 and month 36 and 6.6% in the preceding 12 months. Since the study instructions demanded that new adverse events or a worsening of severity of established adverse events be reported, it appears that eyelash growth is an early reaction to treatment that does not worsen over time.

There were approximately 13% new cases of conjunctival hyperaemia reported in each of the 12-month time periods studied in 192024-014. As observed previously, the reports in the long-term studies were also primarily mild in severity. Conjunctival hyperaemia was not responsible for any discontinuation of bimatoprost QD therapy at either the 2-year or 3-year timepoints.

Comparison of the safety profile of bimatoprost to latanoprost (studies 192024-010 and -019) shows a lower incidence of conjunctival hyperaemia favouring latanoprost. However, the impact on patients appears minimal since the mean satisfaction score reported by patients receiving bimatoprost was not statistically significantly different from that in patients receiving latanoprost.

Furthermore, a review of the incidence of conjunctival hyperaemia over the 6-month period based on slit lamp findings showed that, although the incidence of positive (mild, moderate or severe) findings is higher for bimatoprost than for latanoprost on starting therapy, this incidence falls by month 6 whilst the incidence for latanoprost remains essentially unchanged over the 6-month study period. This is reflected also on reviewing the mean hyperaemia severity grade scores where a decrease from 0.55 at month 1 to 0.42 at month 6 is seen for bimatoprost whilst the equivalent score for latanoprost is steady in the region of 0.3 throughout the time-period. It must be remembered that a score of 0.5 denotes a 'trace' observation. The severity of the conjunctival hyperaemia associated with bimatoprost therefore diminishes over time. It is not of an inflammatory nature with no clinically significant changes in laser flare meter readings seen throughout the 12-month dosing period during which such readings were taken. In addition pre-clinical data suggest that the hyperaemia is primarily a result of vasodilatation.

Of particular importance is the incidence of iridial pigmentation associated with bimatoprost. The incidence was 1.5% at the 12-month stage. There have been no further new cases reported in either of the two subsequent 12-month follow-up periods. Therefore the incidence remains at 1.5% at 3 years. One case was seen in the 6 months comparison with latanoprost.

Although the frequency of increased iris pigmentation is less than other prostaglandin analogues the long-term consequences of this are not known. The MAH was therefore asked by the CPMP to indicate their plans for long term follow-up of patients who have iris pigmentation and also for monitoring for the occurrence of trabecular meshwork pigmentation in long-term treated patients.

The MAH responded that with the purpose of long-term follow-up of patients who have changes in iris pigmentation and to monitor the occurrence of trabecular meshwork pigmentation in long term treated patients the following had been planned:

- In Study 192024-014 a gonioscopy will be performed at Month 48 in the further study extension to Month 48 and compared with that already performed at Month 36.
- A study comparing the amount of pigmentation in the trabecular meshwork obtained in specimen collected during trabeculectomy surgery will be conducted.

The CPMP considered that the amount of data to be obtained of the long-term consequences of the increased iris pigmentation by the planned investigation appears scarce and asked the MAH to provide proposal for a commitment to further study the safety of Lumigan in the first line treatment of raised intraocular pressure.

The MAH outlined the programme intended to further study iris pigment changes, as well as the general safety of bimatoprost in the first line indication. It included:

- Performance of a prospective, observational study to collect safety and efficacy data from patients treated for open angle glaucoma or ocular hypertension with bimatoprost, latanoprost or travoprost. A follow-up of up to 3 years is planned.
- To provide the report from the ongoing masked evaluation to acquire efficacy and safety data from a total of 4 years bimatoprost exposure (study 192024-014)
- To provide the report of the 5-year safety data from Study MM-HTL-001, which enrolled patients who completed study 192024-014 into a 1-year open-label study
- To perform study 192024-029. In this study samples will be obtained of trabecular meshwork at time of trabeculectomy for histological assessment. This will be a masked evaluation of pigmentation and will include assessment of histological evidence of inflammation, degeneration etc. as already described

The MAH committed to the above programme and this was considered acceptable by the CPMP.

5. Overall conclusions and benefit/risk assessment

Quality

The company has developed a product of satisfactory quality in relation to the clinical use, i.e. a buffered, sterile, isotonic solution that is preserved against microbial contamination during storage and use. The manufacturing process has been validated and provides a satisfactory assurance that the product will be sterile when opened for the first time. Methods used for batch control and stability studies have been validated and should ensure a product of reproducible quality.

Preclinical pharmacology and toxicology

Pharmacodynamic studies have been carried out to assess the IOP decreasing effect of bimatoprost. Bimatoprost increases uveoscleral outflow in monkeys and not in dogs but its exact mechanism of action is not known. The applicant has conducted a receptor panel screen with bimatoprost. The results show that bimatoprost has no interaction with cannabinoid receptors (CB_1, CB_2), and over 100 receptor targets, ion channels, and transporters. The prostamide receptor has not been structurally identified. Bimatoprost does not interact with known prostaglandin receptors, including the FP receptor, which is thought to be involved in the decrease of IOP caused by $PGF_{2\alpha}$ analogues such as latanoprost.

Results from a battery of *in vitro* and *in vivo* safety pharmacology studies did not show any pharmacological effects that were not expected for this type of substance.

Based on the preclinical reproduction toxicity results, it is recommended that Lumigan should not be used during pregnancy unless clearly necessary.

Efficacy

Six phase III studies were initially submitted (4 in the original dossier and 2 in the response to List of questions). The trials were conducted in patients with open angle glaucoma, ocular hypertension, pseudoexfoliative glaucoma or pigmentary glaucoma or closed-angle glaucoma with patent iridotomy. Data for a period of a maximum of 12 months (monotherapy) had been presented. In summary, bimatoprost 0.03% in monotherapy was superior to timolol. As part of the response to LoQ the company submitted further 6 and 9 months data on monotherapy and adjunctive therapy (extension study 502) respectively. This study showed a consistent IOP-decreasing effect of bimatoprost qd adjunctively to a topical beta-blocker for up to 12 months. Statistically significant changes from 3-months values in the IOP were also seen in those patients who started with vehicle/beta-blocker switched to bimatoprost/beta-blocker regimen.

Overall, bimatoprost 0.03% qd is effective in lowering IOP in patients with chronic open angle glaucoma and ocular hypertension. In the initial application, efficacy was confirmed for up to twelve months in both monotherapy and adjunctive therapy.

For the subsequent application for first line therapy the MAH submitted two main clinical studies: bimatoprost monotherapy versus timolol and bimatoprost monotherapy versus latanoprost. In addition, two further studies provided supportive data: bimatoprost monotherapy versus a fixed combination and bimatoprost versus adjunctive therapy. A review of all available published literature was also submitted. The submission included evidence for a consistent IOP decreasing efficacy over 36 months of bimatoprost applied once daily. It was demonstrated in comparison with the well-established first line therapy timolol, where a clinically and statistically superior effect was seen. Moreover, a superior effect compared to the established first line prostaglandin agonist latanoprost was shown in a 6 months comparison. In light of the increasing awareness of the significance of achieving low IOP values in the treatment of open angle glaucoma and ocular hypertension these results are important.

Safety

The initial clinical development programme for bimatoprost 0.03% ophthalmic solution consisted of 13 phase I to III studies which provided a safety database of 2326 patients with glaucoma or exposed to a variety of concentrations and dosing regimen of bimatoprost. Of these 1708 ocular hypertension

or normal subjects, including 1708 patients or normal subjects who were patients, 1219 received a concentration/regimen of bimatoprost alone and 489 bimatoprost in combination with a topical beta-blocker. The remaining 618 patients or normal subjects received active control or vehicle.
As part of the response to LOQ the company submitted 12 month safety data from the two monotherapy studies (008 and 009), 9/12 month safety data from the adjunctive therapy extension study 502 as well as 3 months safety data from two phase IIIb studies not previously reported.

Overall, the safety profile would seem acceptable. However, in view of the adverse events pattern being inferior to that of relevant standard approved treatment options (timolol), only the second line therapeutic indication was initially considered appropriate. Apart from certain adverse events that are not considered of major clinical importance, the safety profile of Lumigan is comparable to that of other approved second-line treatment options.

For the subsequent application for first line therapy data were provided for up to 36 months of use. The safety profile seems reassuring regarding the characteristic risk factors (iris pigmentation, intraocular inflammation and cystoid macular oedema). Overall, the safety data provided confirm the established safety profile of Lumigan.

Benefit/risk assessment

Overall, bimatoprost 0.03% qd is effective in lowering IOP in patients with chronic open angle glaucoma and ocular hypertension. Consistent efficacy has been confirmed for up to 36 months as monotherapy and 12 months for adjunctive therapy.

Overall, the safety profile would seem acceptable. The incidence of conjunctival hyperaemia, growth of eyelashes, and eye pruritus was statistically significantly higher with bimatoprost than with latanoprost, however, the discontinuation rates due to adverse events were low and without statistically significant difference.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Lumigan in the treatment of elevated intraocular pressure in chronic glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers) was favourable.