# 1    SCIENTIFIC DISCUSSION

## 1.1    Introduction

Chronic glaucoma is an eye disease characterised by increased intraocular pressure, glaucomatous excavation and atrophy of the optic nerve head, and reduction of the visual field. It is a common disease accounting for a substantial percentage of the cases of blindness in the developed world.

Primary open-angle glaucoma is a chronic, generally bilateral but often asymmetrical disease characterised by a multifactorial optic neuropathy in which there is a characteristic acquired loss of retinal ganglion cells and atrophy of the optic nerve. The aetiology is multifactorial and the elevated intraocular pressure (IOP) is an important risk factor among several others, e.g. inheritance, age, race, myopia and cardiovascular disease. In the European population above the age of 40 years the occurrence is about 1 %, (accelerating with increasing age).

Other characteristics are adult onset, open, normal-appearing anterior-chamber angles and absence of known other (e.g., secondary) explanations for progressive glaucomatous optic nerve change (e.g., pigment dispersion, pseudoexfoliation, iridocorneal endothelial syndrome).

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

The IOP can be lowered by medical treatment, laser surgery, and incisional surgery (alone or in combination). In most instances, topical medications constitute initial therapy. Argon laser trabeculoplasty is an appropriate initial therapeutic alternative and filtering surgery may be an appropriate initial therapy for some patients with moderate or severe glaucoma.

Medical agents that increase aqueous outflow include topical miotics, topical adrenergic derivatives, and prostaglandin analogues. Agents that decrease aqueous production include carbonic anhydrase inhibitors, alpha2-adrenergic agonists and beta-adrenergic antagonists. To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background fluctuations of IOP.

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

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

The indication for Ganfort is the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues. The recommended dose is one drop of Ganfort in the affected eye(s) once daily, administered in the morning. Ganfort consists of a combination of two well-known ophthalmic drugs, timolol (0.5% or 5 mg/mL) and bimatoprost (0.03% or 0.3 mg/mL). The rationale for the development of a topical ocular product that combines a synthetic prostamide (bimatoprost) and a beta-blocker (timolol) in a single formulation for the reduction of IOP by the differential mechanisms of action and complementary pharmacology of the active ingredients, was that the majority of patients with glaucoma or ocular hypertension eventually require adjunctive therapy to control their IOP. Therefore, the fixed combination may lead to increased compliance since it is administered more conveniently than the individual products administered adjunctively. Furthermore, there is an

elimination of the risk of wash-out of the first administered IOP-lowering agent and a reduction in the exposure to the potentially harmful preservative benzalkonium chloride.

The individual active substances are bimatoprost, which was granted approval via centralised procedure under the invented name Lumigan (EU/1/01/205/001-002), and timolol, which are both indicated for lowering IOP. The concentration of timolol in Ganfort is equivalent to the commonly used monotherapy concentration. However, the daily timolol exposure is one half the monotherapy dose, since Ganfort is only to be applied once daily whereas timolol as a monotherapy is typically applied twice daily.

## 1.2    Quality aspects

### Introduction

Ganfort is formulated as sterile preserved aqueous formulation for topical ophthalmic application. This combination product contains bimatoprost 0.03% and timolol maleate 0.68% as active substances. Excipients include also sodium chloride, sodium diphosphate dibasic heptahydrate, citric acid monohydrate, benzalkonium chloride and purified water.

The product is supplied in LDPE bottle.

### Active substance

Two drug substances are used in this fixed combination product, bimatoprost and timolol (as maleate).

Bimatoprost

This active substance has been approved for use in Lumigan via centralised procedure (EU/1/01/205/001-002).

Bimatoprost is a white to off-white powder, hygroscopic, slightly soluble in waterit shows polymorphism, but following the manufacturing process described, polymorph I is obtained. There is no difference in terms of aqueous solubility between the polymorphic forms.

The chemical structure is well characterised, it has 5 chiral centres and it also has cis-trans isomerism, the selected form being (Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(1E, 3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentenyl]-N-ethyl-5-heptenamide.

Bimatoprost is synthesized in 4 steps followed by purification. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. The three-production scale batch data presented showed a reproducible manufacturing process leading to homogeneous batches.

Bimatoprost specifications include tests for physical characteristics, identity (IR, HPLC), assay (HPLC, 97.5-101.0%), physical purity, chemical purity, residual solvents, related substances, moisture (KF), microbial limit.

The tests and limits in the specifications are considered appropriate for controlling the quality of this active substance.

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

Timolol maleate
The drug substance timolol maleate (INN) is an active substance described in the European Pharmacopoeia. It is a white to almost white crystalline powder or colourless crystals. It is soluble in water and in alcohol. It shows optical activity.

The chemistry, manufacturing and control information on timolol maleate have been evaluated by the EDQM and a Certificate of Suitability of the Monograph of the European Pharmacopoeia has been issued. This CEP includes additional test for residual solvents and for related substances by HPLC. Although in the Eur Ph monograph the impurities are determined by a TLC method, the manufacturer used an additional HPLC method, annexed to the Certificate.

Timolol maleate is controlled according to the requirements of the Ph. Eur. Monograph and additional requirements according to the CEP and a microbial limit test (MLT) according to the Ph Eur as the active substance is used in aseptic preparation of the finished drug product.

Batch analysis data of 3 representative batches of timolol maleate are provided. The batches are within the specifications and consistent from batch to batch.

Stability data on 11 production batches covering periods up to 60 months at 25 C 2 C / 60% 5% RH were providedAn annual retest will be applied by the applicant. The re-test period proposed is supported by the stability data provided.

**Finished Product**

- Pharmaceutical Development

The main goal in the development of this ophthalmic solution was to obtain a safe and effective formulation for topical application to the eye that would provide a comfortable dose with minimal risk of irritation. Development studies have been conducted to evaluate the stability of formulation, compatibility of formulation with the container closure system, preservative effectiveness, and ocular tolerability of the formulation. The eye drops are formulated with well-known excipients and the composition is very similar to the already approved Lumigan (bimatoprost) eye drops, apart from timolol maleate content and the adjustment in sodium chloride concentration for isotonicity. Viscosity of the solution is similar to water.

The solution is packaged in a multiple-dose eye drop white bottle and a white tip manufactured from low density polyethylene (LDPE) and a blue cap manufactured from high impact polystyrene (HIPS). This container closure system is the same used in Lumigan.

- Manufacture of the Product

The process selected is similar to the process used in the manufacture of Lumigan eye drops, these including (1) the preparation of the bulk followed by (2) sterile filtration of the bulk product and aseptic filling into pre-sterilised containers.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process in three production-scale batches of each and is satisfactory. The in process controls are adequate for this product.

The 3 commercial batch analysis data provided show that this solution can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this eye drop preparation.

- Product Specification

The product specifications include tests by validated methods for physical appearance, assay of the active substances (HPLC, 95.0-105.0% of label strength in each case), identification of the active substances (HPLC, TLC), benzalkonium chloride assay, benzalkonium chloride identification, impurities (HPLC), pH (Ph Eur), osmolality (Ph Eur), sterility (Ph Eur), efficacy of antimicrobial preservation (Ph Eur), particulate matters (Ph Eur).

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis results of pivotal clinical batches (2), primary stability (3), and supportive stability (15) are included and confirm satisfactory uniformity of the product at release.

- Stability of the Product

The stability studies have been carried out during 12 months at 25ºC/40%RH and 6 months at 40ºC/20%RH on primary stability batches, 24 months at 25ºC/40%RH and 6 months at 40ºC/20%RH on supportive stability batches and 9 months at 25ºC/40%RH and 6 months at 40ºC/20%RH on validation batches in accordance with ICH Guidelines.

The parameters controlled are the same as for release: physical appearance, particulate matter, pH, osmolality, assay of bimatoprost and timolol, degradation products, assay of BAK (benzalkonium chloride), sterility, preservative efficacy and packaging integrity. The control of water loss is included in all the studies but there is no specification of this parameter during the shelf-life.

A photostability study on one supportive stability batch was performed. The light study conformed to ICH option 2 light emission standard exposure (>200 Watts UV and > 1.2 million lux hours of visible light). Results showed that the drug product is well protected in the primary packaging compared to controls.

Freeze/thaw and low/high temperature cycling studies (2 days at -10 to -20°C and 2 days at 40°C) have been also performed on one batch to determine the effect of temperature. The cycling studies data indicate that short excursions to the studied temperature extremes do not adversely affect the quality of the solution.

In use stability studies have been carried out on one commercial batch and on one pilot batch near the end of shelf life, following the relevant ICH guideline. The parameters tested were: physical, chemical and microbiological. The data support the shelf life proposed after the first opening.

Based on available stability data, the proposed shelf life, storage conditions and in-use of the finished product after first opening as stated in the SPC are acceptable.

**Discussion on chemical, pharmaceutical and biological aspects**

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

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

## 1.3    Non-clinical aspects

**Introduction**

**Pharmacology**

- Primary and secondary pharmacodynamics

Studies in dogs and monkeys have been carried out to assess the mechanism of the IOP-lowering action of bimatoprost. In dogs, topically applied bimatoprost did not affect total outflow facility, indicating that bimatoprost does not lower IOP by affecting conventional, trabecular outflow facility. Similarly, in monkeys, bimatoprost had no effect on total outflow facility, but increased uveoscleral outflow by 42%. Fluorophotometric studies showed that bimatoprost 0.1% did not alter aqueous humour inflow in monkeys. The results of these studies suggest that bimatoprost lowers IOP by increasing uveoscleral outflow. The mechanism of action by which bimatoprost reduces IOP in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a non-selective $\beta_1$ and $\beta_2$ adrenoceptor antagonist that lowers IOP by suppressing aqueous humour formation in humans. The mechanism of the ocular hypotensive effect of timolol is predominately by reduction of aqueous humour formation as shown by fluorophotometry and tonography studies in humans and nonhuman primates. Timolol exerts little or no effect on the facility of outflow.

The secondary pharmacodynamics of timolol is well described. Based on receptor screening assays and in vitro tissue preparations, bimatoprost is not expected to interact with prostaglandin receptors and a variety of other receptors, ion channels and transporters. New studies have been performed trying to elucidate the nature of the bimatoprost receptor and the mechanism of action. Currently, the data suggest two hypotheses: bimatoprost may activate a newly identified spliced variant of the FP receptor or it may activate a novel receptor that heterodimerizes with the FP receptor. Interestingly, long-term treatment with both bimatoprost and the prostaglandin $F_{2\alpha}$ agonist latanoprost lead to remodelling of the uveoscleral outflow routes and morphological changes in the trabecular meshwork, providing evidence for the increases in uveoscleral and trabecular outflow.

Whereas $PGF_{2\alpha}$'s main effect in humans is contraction of the uterus, bimatoprost was virtually devoid of uterotonic activity in both the pregnant and non-pregnant human isolated uterus. Species differences were apparent with respect to animal uterine studies. Also in contrast to $PGF_{2\alpha}$, bimatoprost does not induce mitosis. Bimatoprost exhibited no meaningful activity at human thromboxane receptors (TP), thus bimatoprost has minimal potential for activating thromboxane receptors associated with uterine, cardiovascular and airway smooth muscle. *In vitro* studies showed that bimatoprost does not induce relaxation of precontracted, endothelium intact rabbit jugular vein; a preparation in which $PGF_2$ causes pronounced vasorelaxation.

- Safety pharmacology

No safety pharmacology studies have been performed with Ganfort. Nevertheless the safety of bimatoprost and timolol is well characterized and there is nothing to indicate that drug interaction occurs.

*Bimatoprost*

Based on safety studies performed in rats and conscious dogs, bimatoprost is not expected to exert any effect on blood pressure, heart rate, electrocardiogram, or respiration rate. Bimatoprost showed no effect in general activity and behaviour tests and in tests on CNS performed in mice and rats. Bimatoprost exhibited only very low activity in the urinary excretion and digestive system. An ocular surface hyperaemic response was observed during chronic bimatoprost treatment but was not associated with inflammation.

*Timolol*
In humans, topical non-selective β-blockers are associated with mild ocular side effects that include ocular irritation and conjunctival hyperaemia. Timolol maleate 0.5% administered topically or intravenously, decreased basal blood pressure and heart rate of anaesthetised dogs. Timolol may be extensively absorbed systemically after ocular inoculation thus it is contraindicated in patients with bronchial asthma or severe chronic obstructive pulmonary disease, and serious systemic effects such as bradycardia, second- and third-degree atrioventricular block, overt cardiac failure and cardiogenic shock.

Timolol may be extensively absorbed systemically after ocular inoculation and therefore specific warnings are given in the Summary of Product Characteristics (SPC) on the adverse reactions that can be seen after administration of β-blockers. Furthermore, under 4.3 in the SPC, Ganfort is contraindicated in patients with reactive airway disease, sinus bradycardia, second- and third-degree atrioventricular block, overt cardiac failure, cardiogenic shock and patients hypersensitive to the active ingredients or any of the excipients.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed with Ganfort. However the occasional use of artificial tear products or topical decongestant antihistamine was allowed during clinical trials. Consequently, the absence of specific drug interaction studies with Ganfort has been included in section 4.5 of the SPC.

**Pharmacokinetics**

The bimatoprost and AGN 191522 (the C1-metabolite) concentrations in blood/plasma were determined using a HPLC/MS/MS method, whereas the timolol content in blood/plasma was determined using GC/MS/MS.

The provided absorption study is of limited value. Only the absorption into one tissue is investigated and the comparison of ocular absorption is made difficult since the Ganfort absorption study design did not include rabbits treated with bimatoprost and timolol as single-therapies. However, the submitted distribution study covers the area in a satisfactory manner.

[$^3$H]-bimatoprost 0.03% and [$^3$H]-timolol 0.5% were rapidly absorbed and distributed into ocular tissues of rabbits. Radioactivity concentrations were highest in the ocular tissues, which were in close contact with the dosing solution; nevertheless, significant concentrations of [$^3$H]-bimatoprost and [$^3$H]-timolol radioactivity were measured in the iris and ciliary body, which are the sites of pharmacological action. Overall, the pharmacokinetic parameters of [$^3$H]-bimatoprost and [$^3$H]-timolol radioactivity in ocular tissues were similar following single- or combination treatment.

Consequently, even though only a single ocular instillation has been investigated, there is no indication that co-administration of bimatoprost and timolol alters the ocular absorption or distribution of the individual Ganfort components.

Topical administration to the eye represents a highly effective route of systemic delivery, thus bimatoprost and timolol were detected systemically following ocular instillation. In monkeys but not in rabbits, a decrease in systemic bimatoprost exposure was seen after Ganfort treatment when compared to the exposure levels obtained after bimatoprost 0.03% treatment alone. In both rabbits and monkeys, combined treatment with bimatoprost 0.03% and timolol 0.5% resulted in an increased systemic timolol exposure than seen with timolol as single-treatment. The increase in timolol $C_{max}$ was 1.7 and 2.6-fold in rabbits and monkeys, respectively. However, these findings do not cause concern since these phenomena have not been observed in the clinic and therefore have no clinical relevance. Systemic patient $C_{max}$ values for bimatoprost and timolol are 0.064 and 0.618 ng/mL, respectively, which is a bit lower than when the drugs are administered as single-therapies.

No new studies on bimatoprost and timolol metabolism or excretion have been performed. The metabolism of bimatoprost and timolol differ and are therefore not expected to affect or alter one another.

Daily IV injections of bimatoprost did not significantly affect any of the hepatic microsomal enzyme activities at systemic exposures 4000 times greater than that seen in humans after ophthalmic administration. Therefore, it is not likely that bimatoprost will give rise to drug-drug interactions involving cytochrome P450 mediated metabolism. Furthermore, the systemic exposure of bimatoprost after ocular administration is negligible. Timolol is metabolised by CYP2D6, which is well-characterized with respect to pharmacokinetic drug interactions. Systemic exposure levels in clinical trials showed no signs of pharmacokinetic interaction between bimatoprost and timolol. Altogether, it is deemed acceptable that no *in vivo* drug-drug interaction studies have been performed.

**Toxicology**

- Single dose toxicity

The single-dose toxicity of bimatoprost (alone) was evaluated in intraperitoneal (IP) and IV studies in mice and rats. IP administration of 96 mg/kg in mice and IV administration of up to 3 mg/kg in rats produced no adverse effects.

The $LD_{50}$ of a single oral dose of timolol was 1190 mg/kg in mice, 900 mg/kg in rats.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies performed in rabbits and monkeys compared the findings made after ocular administration of bimatoprost 0.03% and timolol 0.5% as single-therapies with the findings made in the Ganfort treatment group. The only treatment related effect seen in the one-month rabbit study was ocular discomfort in rabbits treated with timolol, whereas no treatment-related findings were made in a three-month rabbit study. The key findings made in a six-month monkey study included increased iridial pigmentation in the bimatoprost treatment group during weeks 4, 13, and 26. An increase in iridial pigmentation was also noted at week 26 in monkeys treated with Ganfort, thus iridial pigmentation was delayed in monkeys treated with Ganfort when compared to bimatoprost as a single-therapy. There was no difference in severity of these changes between groups. According to the applicant, the increased iris pigmentation is caused by an increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. Iridial pigmentation is also observed in the clinic and thus the adverse effect is mentioned in the SPC under section 4.4. Altogether, no unexpected findings were made after repeated ocular administration of Ganfort at doses that reached systemic exposures (AUC) up to 200 and 9-fold higher than seen in patients for bimatoprost and timolol, respectively.

- Genotoxicity *in vitro* and *in vivo*

Bimatoprost was negative for genotoxic potential in a battery of tests endorsed by ICH, including Salmonella/Escherichia coli Mutagenicity Assay, Reduced Volume L5178Y/TK +/- Mouse Lymphoma Mutagenesis Assay, and the *in vivo* Mouse Micronucleus Assay

Timolol maleate was negative in Ames assay using Salmonella typhimurium strains TA98 and TA100. Timolol maleate was negative for mutagenicity in the *in vitro* neoplastic cell transformation assay, mouse micronucleus assay and mouse cytogenetic assay.

- Carcinogenicity

The carcinogenic potential of bimatoprost was evaluated in two lifetime (104 weeks) oral studies, one in mice and one in rats. There was no evidence of carcinogenic potential in mice or rats at systemic exposures that achieved 1300 and 2000-fold, respectively, the exposure in humans given the combination ocular regimen. A dose-related increase in the number of vacuolated corpora lutea was observed in female rats.

In a two-year oral study of timolol maleate in rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in males at 300 mg/kg/day, which was approximately 51,000-times the daily dose of timolol in Ganfort at the ocular clinical regimen.

- Reproductive and developmental studies

In rats, bimatoprost affected gestation and prenatal development, manifested as reduced gestation length, late resorption and foetal death, postnatal mortality, and reduced pup body weight with a safety margin of 94. When bimatoprost was administered to mice during pregnancy an increased incidence of late abortions and early delivery were seen with a safety margin of 18.

Furthermore, human data from epidemiological studies suggest that a risk of intra-uterine growth retardation may exist following exposure to systemic beta-blockers. In one case report, bradycardia and arrhythmia occurred in the foetus of a woman who was being treated with timolol eye drops.

Based on these findings, it is not recommended to use Ganfort during pregnancy.

- Local tolerance

In ocular toxicology studies, transient ocular discomfort and conjunctival hyperaemia, but no signs of inflammation were observed in rabbits and dogs that received bimatoprost. No signs of iritis/uveitis were observed in chronic toxicological studies of bimatoprost in rats and monkeys. The mechanism of hyperaemia related to bimatoprost treatment appears to occur by endothelial-mediated vasodilatation and is not associated with inflammation in laboratory animals.

- Other toxicity studies

A variety of container/closure extractables have been identified, i.e. benzyl alcohol, phenol, benzoic acid, oligomers of polyethylene glycol monobenzoate esters (E8 and E9) and the still unidentified peaks E6, E10, E11 and E12. A literature evaluation of benzyl alcohol, benzoic acid and the oligomers of polyethylene glycol monobenzoate esters showed that safety margins for these compounds were multiple folds above human exposure when the intended clinical dose of bimatoprost is given. Phenol and the unidentified impurities E6, E10, E11 and E12 have not been qualified and their concentration should therefore not exceed a limit of 3 ppm (ICHQ3B).

The potential antigenicity of bimatoprost was evaluated using a passive cutaneous anaphylaxis assay (PCA) in rats and guinea pigs, and a systemic anaphylaxis assay in guinea pigs. Intraperitoneal, intradermal or intravenous administration of bimatoprost did not produce dermal or systemic antigenic reactions, and there were no other drug-related effects. The potential to elicit a delayed dermal contact hypersensitivity response was evaluated in guinea pigs. None of the guinea pigs induced intradermally with bimatoprost responded to topical challenges of bimatoprost.

The pharmacological activity of two minor impurities in the bimatoprost bulk drug material, 15 - AGN 192024 and 5,6-trans AGN 192024, and a minor impurity and degradant, 15-oxo AGN 192024, were determined *in vitro* preparations. The results of these studies suggest that these three potential synthetic impurities/degradants contribute minimally to the ocular hypotensive activity of bimatoprost and are not likely to be associated with ocular side effects.

**Ecotoxicity/environmental risk assessment**

The $PEC_{SURFACEWATER}$ values from the Phase I exposure assessment of bimatoprost and timolol were calculated to $8.4 \times 10^{-6}$ and $1.4 \times 10^{-5}$ µg/L, which is significantly less than the action limit of 0.01 µg/L described in the draft guideline "Guideline on the Environmental Risk Assessment of Medicinal products for Human use". Ganfort is unlikely to pose a risk to the environment.

## 1.4    Clinical aspects

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

The applicant has provided a statement that clinical trials conducted outside the European community met the ethical requirements of Directive 2001/20/EC.

**Pharmacokinetics**

The applicant has provided three clinical studies supporting the pharmacokinetic  profile of bimatoprost  0.03%/ timolol 0.5% combination eye drops (referred to as Combination) following ocular administration to healthy subjects (Phase I Study 192024-503T) and to patients with glaucoma or OHT (Phase III Studies 192024-018T and 192024-021T).

Study 192024-503T
The design of study 192024-503T was aimed to investigate the pharmacokinetic profile of the combination in 17 healthy volunteers. This study consisted of a 7-day, three-period cross over design in which once daily morning administration of the Combination was compared to once daily morning dosing of bimatoprost 0.03% (Lumigan) and once daily morning dosing of Timolol (Timoptol) and a wash-out period of 7 days between treatments.

According to the results provided by the applicant when coadministered with timolol as combination, mean bimatoprost Cmax value was 0.064 ng/mL with a Tmax value at 0.11 hr and was below 0.025 ng/mL at 20 minutes post-dose, which indicates a reduction on bimatoprost levels with respect the administration of Bimatoprost 0.03% monotherapy (Cmax 0.071 ng/mL, Tmax 0.12 hr).

Bimatoprost 0.03% monotherapy is administered in the evening while the Combination has a morning administration.

With respect to timolol pharmacokinetic parameters, during the administration of 0.5% timolol monotherapy for 7 days, the mean Cmax was 0.868 ng/mL with a Tmax value of 0.62 hr post-dose although when coadministered as combination, mean timolol Cmax value decreased 29% to 0.618 ng/mL, but the half-life remained unchanged at 10.78 hr.

During the Phase III studies supporting Ganfort MAA (Studies 192024-018T and 192024-021T) therapeutic drug monitoring was performed in order to assess the pharmacokinetic profile of the combination in conjunction with that previously described in healthy volunteers. The design of studies 192024-018T and 192024-021T were primarily aimed to investigate the efficacy/safety of the combination and confirm the pharmacokinetic profile in the  target population. These studies consisted of 12-month, 3-arm parallel design in which one daily morning administration of the Combination was compared to once daily evening dosing of bimatoprost 0.03% (Lumigan) and twice daily morning and evening dosing of Timolol.

Taking into account that the pharmacokinetic results obtained in the pivotal studies were only aimed to monitor the plasma concentration of the active substances (blood concentration at minute 5) and that no pharmacokinetic parameters have been provided, the complete pharmacokinetic profile of the combination relies on Phase I study 192024-503T (17 healthy volunteers).

Study 192024-018

The mean blood concentrations of bimatoprost in the Combination group obtained from Months 3, 6, and 12 were 0.0485 ng/mL, 0.0479 ng/mL, and 0.0514 ng/mL, respectively.

Moreover, no statistical comparison was performed on the bimatoprost blood concentrations between the combination and bimatoprost groups due the fact that, in the bimatoprost group, patients were dosed on the evening of the day before the sample collection day (approximately 12 hours after dosing), and therefore the blood bimatoprost concentrations were generally below the limit of quantification.

One of the main objectives of this study was the comparison between both treatments and the fact that bimatoprost monotherapy (Lumigan) has an evening posology.

The 5-minute postdose mean timolol plasma concentrations were larger in the Timolol group than in the combination group at all follow-up timepoints, and were statistically significantly higher ($p \leq 0.0154$) at Months 3, 6, and 12, with an overall statistical significance of $p = 0.0005$. This is expected, as the twice-daily regimen should result in a higher peak concentration.

The incremented concentration of timolol monotherapy versus timolol in the combination have been justified by the applicant with the different posology administered in both arms, timolol monotherapy was administered twice a day (which is the recommended posology in terms of efficacy) while the combination had a morning administration. This justification is considered acceptable; the administration of timolol twice a day is considered adequate to compare the efficacy of both treatments although no pharmacokinetic comparisons are allowed with this design.

Study 192024-021

The Months 3, 6, and 12 mean blood concentrations of bimatoprost in the Combination group were 0.0619 ng/mL, 0.0618 ng/mL, and 0.0489 ng/mL, respectively, with no statistically significant differences over time. Moreover, the 5-minute post-dose mean timolol plasma concentrations were larger in the Timolol group than in the Combination group at all follow-up timepoints and were statistically significantly higher ($p \leq 0.036$) at Months 3 and 12, with an overall statistical significance ($p = 0.0123$)

The Phase I pharmacokinetic study (192024-503T) was conducted with Formulation 9264X (Isotonic), which is slightly different to the intended commercial formulation (the sodium chloride concentration was reduced to reduce the amorality) However, the formulation 9374X used in the Phase III clinical studies is the same as the product intended for marketing.

The applicant has not developed any studies aimed at demonstraingt the potential differences in the absorption/efficacy of both formulations.

Bimatoprost major metabolites in blood were AGN 191522 (the C1 metabolite) (5.9%), M-12 (bimatoprost glucuronide) (9.4%), and M-14 (another bimatoprost glucuronide) (18.1%). The two glucuronides of bimatoprost are not considered active and therefore have not been investigated by the applicant.

The concentration measurements of AGN 191522 (the potentially pharmacologically active C-1 acid metabolite of bimatoprost) have been determined in all the human pharmacokinetic studies supporting the Ganfort Marketing Authorisation Application (MAA) [192024-503T (healthy volunteers), 192024-018T and 192024-021T (Target population)]. However, no pharmacokinetic analysis has been performed due the fact that AGN 191522 concentrations were uniformly below 0.05 ng/mL in all blood samples (Study 192024-503T).

Taking into account that the limit of quantification established in Lumigan MAA as well as the proposed dose of bimatoprost in the combination schedule are the same, the absence of a complete description of AGN 191522 pharmacokinetic profile supporting Ganfort MAA could be considered acceptable.

- Special populations

The applicant has not developed specific studies in patients with renal or hepatic impairment and a recommendation of caution in use has been included in the SPC.

The applicant has performed statistical analyses in Phase III studies to examine the effects of demographic variables on drug concentrations in both trials, the applicant concludes that these findings are considered exploratory in nature and so the results are not discussed. However, some of these findings seem to show potential differences in the combination pharmacokinetic parameters vs. monotherapies related to gender.

With regard to the elderly, the applicant justifies the absence of specific subgroup analysis by noting that the mean age of the long-term Phase III population was 61.0 years with a significant proportion (37.6%) falling into the > 65 years category. Moreover, the applicant relies on the fact that the individual products, as monotherapy, do not have a requirement for dose adjustment in the elderly population.

- Pharmacokinetic interaction studies

The applicant has not conducted *in vitro* interaction studies since the Combination is not expected to have a different safety profile to the individual agents (See Non-Clinical section).

Moreover the absence of *in vivo* drug-drug interactions studies with other agents is justified by the applicant by the fact that in the bimatoprost monotherapy (Lumigan MAA) Phase III trials, patients typically received concomitant medication, and no particular safety events were attributed any one group of concomitant medication. This could be supported with the low drug concentrations of bimatoprost (< 0.2 ng/mL) following ocular dosing.

With regard to the potential drug-drug interaction between the both components of the combination, the applicant concludes that the mean pharmacokinetic parameter values and their associated variabilities were very similar between the treatments, indicating no evidence of drug-drug interactions.

**Pharmacodynamics**

- Mechanism of action

Bimatoprost is a synthetic prostamide, structurally related to prostaglandin F (PGF) that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesized substances called prostamides and reduces intraocular pressure in man by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol maleate is a 1 and 2 adrenoreceptor non-selective blocker that does not have significant intrinsic sympathomimetic activity or membrane stabilizing activities. Blocking the beta adrenoreceptors results in reduction of the intracellular second messenger, cAMP, believed to be involved in aqueous humour dynamics. Timolol does not have any effect on the outflow mechanism and exerts its effect on IOP by reducing aqueous humour production (Robinson et al, 1993; Yablonski et al, 1978). The effect on IOP appears to outlast the effect on aqueous humour.

- Primary and Secondary pharmacology

The pharmacology of bimatoprost and timolol are well established and have been demonstrated by studies included in the Lumigan Marketing Authorisation Application and described in the Timoptol SPC. No new clinical pharmacology studies were performed with the Combination, and this could be considered acceptable.

With regard to pharmacodynamic interactions, the potential interaction of timolol with other antihypertensive drugs (addictive effects with potential consequences of hypotension and/or

bradycardia) or antidiabetic drugs (hypoglycaemia) has been studied. This potential interaction have been adequately included in the SPC (Section 4.5)

**Clinical efficacy**
A clinical development programme was conducted to evaluate the efficacy and safety of the bimatoprost 0.03%/timolol 0.5% eye drops combination, henceforth known as the Ganfort combination, for the reduction of elevated intraocular pressure (IOP) in patients with glaucoma or ocular hypertension (OHT).

The Phase III clinical development programme comprised 4 studies:
- Studies 192024-018T, 192024-021T, and 192024-504T were designed to compare the safety and efficacy of the Combination with that of the individual components administered as monotherapy. These were bimatoprost 0.03% eye drops (Lumigan; henceforth known as bimatoprost) and timolol 0.5% eye drops (henceforth known as timolol).
- Study 192024-026T compared the safety and efficacy of the Ganfort combination to adjunctive (concurrent) use of bimatoprost along with timolol (referred to as Concurrent treatment).

The studies were designed in accordance with the European regulatory guideline for comparing fixed combination medicinal products with the individual components (European Commission, 3CC10a, 1996). Thus, the use of active control groups rather than a placebo group was considered appropriate for these studies.

The data for the 2 identically designed studies, 192024-018T and 192024-021T, were also pooled and the results of this analysis are summarised.

- Dose response study
Since only one dose and regimen of the Ganfort combination was studied, no drug-dose relationship to response was established.

The Ganfort combination therapy consists of bimatoprost 0.03% and timolol 0.5%. In the clinical studies, the dosing regimen for the Ganfort combination was one drop daily administered once daily in the morning.

Timolol 0.5% was selected as the preferred dose in the Ganfort combination product, as the 0.25% concentration is considered to be of minimal value in the poorly controlled patient. In addition, the use of timolol 0.5% once-daily has been shown to provide a beneficial effect on IOP over a 24-hour period, an effect that was less pronounced with the 0.25% concentration (Zimmerman and Kaufman, 1977).

The applicant has provided a justification for the proposed morning posology based on the results of the 24-hour IOP diurnal curve in the glaucomatous patient according to the literature and the evidence of a comparable daytime IOP control regardless of Bimatoprost morning or evening dosing (Lumigan clinical development programme).

However, although no direct comparison between dose timing has been performed, no relevant differences between the morning and evening administration are expected. Sections 4.2 & 5.1 of the SPC recommend a morning dosing of Ganfort, however, if necessary for patient compliance evening dosing may be considered.

- Main studies
A multicentre, double-masked, randomised, parallel group design was used for all studies. Treatment allocation was randomised and double-masked in order to reduce bias.

Studies 192024-018T and 192024-021T were 12-month studies conducted in the US and Canada and had a common design. Study 192024-504T was a 12-week study conducted in Europe, Australia, New Zealand and South Africa, and Study 192024-026T was a 3-week study conducted in North America and Europe.

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| Study/Report No. | Study Type | Population (ITT) | Key Features |
|---|---|---|---|
| 192024-018T | Long-term efficacy and safety<br><br>Statistical testing for **superiority** | OHT or glaucoma<br>(N = 520) | Ganfort combination compared with Bimatoprost, and Timolol<br><br>Double-masked, 3-arm parallel-group<br><br>Once daily, morning dosing of the Ganfort Combination<br><br>3-month primary analysis period followed by 9-month masked follow-up period |
| 192024-021T | Long-term efficacy and safety<br><br>Statistical testing for **superiority** | OHT or glaucoma<br>(N = 541) | Ganfort combination compared with Bimatoprost, and Timolol<br><br>Double-masked, 3-arm parallel-group<br><br>Once daily, morning dosing of the Ganfort combination<br><br>3-month primary analysis period followed by 9-month masked follow-up period |
| 192024-504T | Efficacy and safety<br><br>Statistical testing for **superiority** | OHT or glaucoma<br>(N = 458) | Ganfort combination compared with Bimatoprost, and Timolol<br><br>Double-masked, 3-arm parallel-group<br><br>Once daily, morning dosing of the Ganfort combination<br><br>12 weeks |
| 192024-026T | Efficacy and safety<br><br>Statistical testing for **non-inferiority** | OHT or glaucoma<br>(N = 445) | Ganfort combination compared with Bimatoprost and Timolol dosed concurrently (adjunctively) and with Bimatoprost monotherapy<br><br>Double-masked, 3-arm parallel-group<br><br>Once daily, morning dosing of the Ganfort combination<br><br>3 weeks |

METHODS

*Study Participants*
The patient population selected in the Phase III studies differed somewhat.

**Studies 192024-018T and -021T**
The studies enrolled adult patients diagnosed with OHT, chronic open-angle glaucoma, or chronic angle-closure glaucoma with a patent iridotomy and requiring bilateral treatment. Those with inadequately controlled IOP ($\geq$ 18 mm Hg in at least 1 eye) on current medication or treatment naïve (IOP $\geq$ 24 mm Hg in at least 1 eye) patients at the prestudy visit (Hour 0 and Hour 2) were eligible.

Qualifying Hour 0 and Hour 2 IOPs must have been from the same eye. The baseline (Day 0, Hour 0) inclusion criteria were post-washout morning IOP $\geq$ 24 mm Hg in at least 1 eye, and best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity equivalent to a Snellen score of 20/100 or better in each eye.

Although patients treated with topical ophthalmic beta-blocker medication within the previous 6 months prior to baseline were excluded from entry into the study, patients inadequately controlled on prostaglandins and prostamides were eligible.

**Study 192024-504T**

This study randomised patients who were insufficiently responsive to beta-blockers.

Patients with glaucoma or OHT whose IOP following run-in on beta-blocker shows inadequate control (IOP 20 to 30 mmHg at hour 0 in one or both eyes. Post wash out Day 0 hour 0 IOP at least +4 mmHg greater than the run-in Hour 0 IOP in the same eye.

This different patient population to the one used in Studies 192024-018T and -021T was selected because it was more akin to the European patient population that would be considered for a new glaucoma combination therapy (in keeping with the prescribing guidelines applicable at the time the study was set up, ie, addition of an antiglaucoma agent if the beta-blocker was unsuccessful).

### Study 192024-026T
This study recruited only patients with glaucoma or OHT in both eyes and requiring bilateral treatment, and only patients naïve to prior IOP-lowering therapy.

It is well established that open-angle glaucoma, other than primary, comprises a small proportion of the population. The patient population from this clinical development programme is no exception with pigmentary, pseudoexfoliative and residual (patent iridotomy) glaucoma seen in at least one eye in the following number of patients:

| Study # | Patients (% of total) | |
|---------|------------------------|------------------|
| | OD | OS |
| 192024-018T | 16  (3.1%) | 16 (3.1%) |
| 192024-021T | 11  (2.0%) | 9   (1.7%) |
| 192024-504T | 45  (9.8%) | 47 (10.3%) |

Treatments, randomisation and blinding (masking)
All studies were randomised, double masked and used the bimatoprost vehicle as "placebo".

### Studies 192024-018T and -021T
Qualified patients were enrolled and assigned to 1 of 3 masked treatment groups (the Ganfort combination, Bimatoprost, or Timolol) based on a 2:1:1 allocation.

For patients in the Ganfort combination group, the combination was administered once daily in the morning, with the vehicle administered in the evening to maintain proper masking against timolol. For patients in the Bimatoprost group, the bimatoprost 0.03% ophthalmic solution was administered once daily in the evening, with the vehicle administered in the morning to maintain proper masking against timolol. For patients in the Timolol group, timolol was administered at both the morning and evening administrations. Patients began study medication dosing in the evening of the day 0 (baseline) visit.

These clinical trial were  12-month studies with a 3-month primary study period and a 9-month masked extension period. The studies were unmasked at month 3 for the analysis of the 3-month data for regulatory filing in the US. Special efforts were made to avoid biasing the conduct of the final 9 months of the studies. The treatment identity and the results of the 3-month data analyses were not revealed at any investigational center prior to study completion. Clinical personnel involved with the daily monitoring of the trial remain masked to the 3-month data during the conduct of the remaining 9 months of the study.

### Study 192024-504T
Qualified patients were assigned to masked treatment groups in a 1:1:1 ratio according to the randomisation schedule.

For patients in the Ganfort combination group, the Combination eye drops were administered QD in the morning, with the vehicle administered in the evening to maintain proper masking against timolol. For patients in the Bimatoprost group, the Bimatoprost eye drops were administered QD in the evening, with the vehicle administered in the morning to maintain proper masking against timolol.

For patients in the Timolol group, timolol eye drops were administered at both the morning and evening dosing times

**Study 192024-026T**
Patients were assigned to masked treatment groups with Ganfort combination, Concurrent, or Bimatoprost based on a 2:2:1 allocation ratio at each study site. Randomisation was stratified by baseline IOP averaged from both eyes into 2 groups, IOP ≤ 26 mm Hg or IOP > 26 mm Hg.

For patients in the Ganfort combination group, the Ganfort combination eye drops were administered QD in the morning, with the vehicle administered twice in the evening to maintain proper masking against timolol. For patients in the Concurrent group, the morning dose was timolol and the evening dose was bimatoprost followed by timolol. For patients in the Bimatoprost group, the morning dose was vehicle and the evening dose was bimatoprost followed by vehicle to maintain masking.

The possible shortcomings of the masking due to the same vehicle, namely the bimatoprost vehicle, used with both the Ganfort combination and with bimatoprost were discussed briefly by the applicant. The only minor difference between the bimatoprost vehicle and the Ganfort combination eye drops (beyond removal of the drug substances) is the slight reduction in sodium chloride concentration in the Ganfort combination eye drops formulation. This minor difference was considered unlikely to influence the masking.

*Objectives*

| Study | Objective |
|---|---|
| **Study 192024-018T** | To compare the safety and efficacy of the bimatoprost 0.03%/timolol 0.5% combination ophthalmic solution once daily with that of timolol 0.5% ophthalmic solution monotherapy twice daily and bimatoprost 0.03% ophthalmic solution once daily administered for 3 months (with a 9-month, masked extension) in patients with glaucoma or ocular hypertension. |
| **Study 192024-021T** | To compare the safety and efficacy of the bimatoprost 0.03%/timolol 0.5% combination ophthalmic solution once daily with that of timolol 0.5% ophthalmic solution monotherapy twice daily and bimatoprost 0.03% ophthalmic solution once daily administered for 3 months (with a 9-month, masked extension) in patients with glaucoma or ocular hypertension. |
| **Study 192024-504T** | To compare the efficacy and safety of bimatoprost/timolol fixed combination once-daily (QD) (dosed in the morning) with that of bimatoprost 0.03% QD (dosed in the evening) monotherapy ophthalmic solution and timolol 0.5% twice-daily (BID) monotherapy ophthalmic solution administered for 12 weeks in patients with glaucoma or ocular hypertension with an elevated intraocular pressure (IOP) on beta blocker therapy alone. |
| **Study 192024-026T** | To evaluate the safety and efficacy of bimatoprost 0.03%/timolol 0.5% combination ophthalmic solution once daily (QD) (hereafter referred to as the Ganfort combination) with that of bimatoprost 0.03% QD and timolol 0.5% twice daily (BID) ophthalmic solutions dosed concurrently (hereafter referred to as Concurrent) for 3 weeks in treatment-naïve patients with glaucoma or ocular hypertension. The bimatoprost 0.03% ophthalmic solution QD treatment arm (hereafter referred to as bimatoprost) was used for validation of study outcomes only. |

*Outcomes/endpoints*
The same efficacy parameters were applied, but the choice of the primary end points varied across the studies:
▪ Study 192024-018T, the primary efficacy endpoint was the percentage of patients achieving the adjusted target IOP <18 mm Hg (adjusted for central corneal thickness)

- Study 19202-021T used the mean change from baseline in IOP
- Study 192024-504T applied the change in mean diurnal IOP
- Study 192024-026T used the mean IOP values as primary efficacy criterion

Among the secondary endpoints were mean IOP values, mean change in IOP, mean diurnal IOP, the proportion of patients achieving target IOP < 18 mm Hg, or > 20 % decrease from baseline IOP in the studies.

**Table          Efficacy Parameters Analysed in Clinical Studies**

| Study | Efficacy Parameters | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Mean IOP values** | **Change in IOP** | **Mean diurnal IOP[a]** | **Change in mean diurnal IOP[a]** | **Target IOP[b] > 20% decrease** | **Target diurnal IOP[a, b] > 20% decrease** | **Target IOP[b] of < 18 mm Hg** | **Target IOP category analysis (< 14 mm Hg, 14 to 17.5 mm Hg, and > 17.5 mm Hg)** |
| **192024-018T** | X | X | | | | X | X | X |
| **192024-021T** | X | X | | | X | X | X | X |
| **192024-504T** | X | X | X | X | X | X | X | |
| **192024-026T** | X | X | X | X | | X | | |

Source: individual CSRs

a  Diurnal IOP = average of Hour 2, Hour 0 and Hour 8 IOPs

b  The number (%) of patients who achieved the target IOP parameter

*Sample size*
See Table          Patient Disposition: All Efficacy Studies

Studies 192024-018T and -021T: in each study, planned enrolment was for 480 patients in order to have 360 patients complete the 12-month study period (assuming a 25% drop-out rate).
- 192024-018T
Four hundred and eighty patients were planned; 520 patients were enrolled in the study, with 261 patients randomized to the Ganfort combination, 129 patients randomized to Bimatoprost, and 130 patients randomized to Timolol groups. There were 450 patients who completed through the month 12 visit of the study.

- 192024-021T
Four hundred and eighty patients were planned; 541 patients were enrolled in the study, with 272 patients randomized to the Ganfort combination, 136 patients randomized to Bimatoprost, and 133 patients randomized to Timolol groups. There were 473 patients who completed through the month 12 visit of the study.

**Table**            **Patient Disposition: All Efficacy Studies**

| Category n (%) | Pooled 192024-018T and 192024-021T | | | 192024-504T | | | 192024-026T | | |
|---|---|---|---|---|---|---|---|---|---|
| | Combination | Bimatoprost | Timolol | Combination | Bimatoprost | Timolol | Combination | Concurrent | Bimatoprost |
| Randomised | 533 | 265 | 263 | 155 | 148 | 156a | 178 | 177 | 90 |
| ITT population | 533 | 265 | 263 | 155 | 148 | 155 | 178 | 177 | 90 |
| PP population | 511 | 257 | 252 | 141 | 135 | 149 | 171 | 165 | 87 |
| Safety population | 533 | 265 | 263 | 152 | 147 | 154 | 176 | 176 | 90 |
| Completed (%) | 468 (87.8%) | 225 (84.9%) | 230 (87.5%) | 146 (94.2%) | 143 (96.6%) | 152 (98.1%) | 172 (96.0%) | 170 (96.0%) | 88 (97.8%) |
| **Discontinued due to:** | | | | | | | | | |
|   Lack of efficacy | 8 (1.5%) | 3 (1.1%) | 6 (2.3%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
|   AE | 37 (6.9%) | 26 (9.8%) | 9 (3.4%) | 7 (4.5%) | 3 (2.0%) | 2 (1.3%) | 3 (1.7%) | 3 (1.7%) | 1 (1.1%) |
|   Administrative reason | 10 (1.9%) | 7 (2.6%) | 15 (5.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 3 (1.7%) | 0 (0.0%) |
|   Protocol violation | 5 (0.9%) | 2 (0.8%) | 1 (0.4%) | 1 (0.6%) | 2 (1.4%) | 1 (0.6%) | 1 (0.6%) | 1 (0.6%) | 1 (1.1%) |
|   Other | 5 (0.9%) | 2 (0.8%) | 2 (0.8%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) |

Source: Section 5.3.5.1, 192024-504T, M5, vol 19, and 192024-026T CSRs, M5, vol 26, and Section 5.3.5.3, Pooled Efficacy Tables for Studies 192024-018T/-021T, M5, vol 28

a   One patient, who was randomised to Timolol, was excluded from all analyses due to misconduct identified at the investigator site before database lock

*Statistical methods*
**Studies 192024-018T and -021T**
An ITT (intent-to-treat) population consisting of all randomised patients in both studies was used for the efficacy analyses.  Analyses were performed for the primary efficacy variable, IOP, using the ITT population (all randomised patients) with last observation carried forward (LOCF), and the per protocol (PP) population with observed cases.  Comparisons were made between the Ganfort combination and each of the 2 monotherapies in a pairwise fashion using contrasts from the ANOVA model, at the 0.05 significance level.

For some of the efficacy parameters, the IOP measurements were also adjusted for corneal thickness based on the Ehlers' method (referred to as the "adjusted IOP").

**Study 192024-504T**
The mean change from baseline in diurnal IOP was the primary efficacy variable and the analysis was performed on the ITT population using LOCF.  Treatment comparisons were made between the Ganfort combination therapy and the individual component groups, and were tested using contrasts from a 2-way ANOVA model with fixed effects for treatment and investigator.  A PP analysis of the primary efficacy variable, mean change from baseline in diurnal IOP, was also performed.

**Study 192024-026T**
An ITT population of all randomised patients was used for efficacy analyses and summaries of demographic and baseline measurements.  The primary comparison of IOP between the Ganfort combination and Concurrent was analysed using non-inferiority and statistical superiority tests.

As is particularly relevant for non-inferiority analyses, corresponding efficacy analyses were also performed using the PP population.

RESULTS

*Recruitment*
The studies recruited patients with OHT and all forms of chronic open angle glaucoma, including primary open-angle, pseudoexfoliative, pigmentary, and chronic angle closure glaucoma with patent iridotomy in each eye.  In addition, patients with mixed pathology were also recruited.

For Study 192024-026T, both eyes needed to be eligible with an IOP asymmetry of no greater than 5 mm Hg, thereby ensuring consistency of disease between eyes.

For Studies 192024-504T, -018T, and -021T, only one eye needed to be eligible, although both eyes needed to require IOP-lowering therapy.

*Conduct of the study*
According to the applicant, all clinical studies were conducted in accordance with current Good Clinical Practice (GCP) guidelines. Studies conducted outside the European Union met the ethical requirements of Directive 2001/20/EC.

However, during Study 192024-504T, prior to database lock, the applicant comments that sufficient evidence of misconduct was discovered at one site to justify the exclusion of data generated by this centre. The site had only randomized one patient. Analyses of both efficacy and safety were performed excluding the data generated from this one patient. Additional analyses of demography, primary efficacy and adverse event incidence were also performed, for comparative purposes, with this patient included.

In addition, prior to database lock, the primary endpoint for Study 192024-018T was amended from the mean change from baseline IOP, to the incidence of patients achieving adjusted target IOP at all follow-up timepoints. The change was caused by the results from the Advanced Glaucoma Intervention Study (AGIS-7) (Am J Ophthalmol 2000; 130:429-440).

*Baseline data*
Study 192024-018T
Overall, the mean age of patients was 59.4 years (ranging from 22 to 91 years). There were more females (53.3%) than males, the majority of the population was Caucasian (72.1%) and the most common iris colour was brown (44.4%).

Study 192024-021T
The female to male gender ratio was 51.9 %: 28.1%. The mean age was 62.4 years (ranging from 24 to 90 years).

The distribution of diagnoses was 52.9 % for glaucoma, 44.4 % for ocular hypertension and 2.8 % for mixed diagnosis, similarly distributed in the treatment groups.

Study 192024-504T
The female to male gender ratio was 62.4 %:37.6 % The mean age was 61.5 years (ranging from 25 to 87 years).

The mean diurnal IOP was 27.36 mm Hg, 26.97 mm Hg, and 27.19 mm Hg in the Ganfort combination group, the bimatoprost and the timolol group, respectively. Patients with a glaucoma diagnosis encompassed 87.8 %, 10.5 % had ocular hypertension and 1.77 % had a mixed diagnosis.

Study 192024-026T
The mean age was 59.8 years (ranging from 18 to 87 years). The female to male ratio was 55.3 %:44.7%.

The mean diurnal IOP values at baseline were similar across the treatment groups: 24.9 mm Hg, 25.2 mm Hg, and 25.0 mm Hg in the Ganfort combination group, the bimatoprost and the timolol group, respectively.

*Numbers analysed*
See Table      Patient Disposition: All Efficacy Studies

*Outcomes and estimation*

**Study 192024-018T**
Results of the primary endpoint, the percentage of patients who achieved a target IOP < 18 mm Hg is shown below. The difference between the Ganfort combination and bimatoprost is not statistically significant, as opposed to the difference between the combination and timolol.

The PP-analyses confirmed the ITT-analyses.

**Table**    Study 192024-018T: Percentage of Patients Achieving Target IOP < 18 mm Hg at All Follow-Up Timepoints (ITT)

| Achieved Target IOP < 18 mm Hg | Combination N = 261 | Bimatoprost N = 129 | Timolol N = 130 |
|---|---|---|---|
| Adjusted | 61.7% | 57.4% | 48.5% |
| Unadjusted | 22.6% | 16.3% | 6.9% |

Source: Section 5.3.5.1, Report 192024-018T, Tables 14.2-5 and 14.2-6.

Note: IOP measured at all follow-up timepoints. Adjusted IOP = IOP measurement adjusted for corneal thickness using Ehlers' approach.

Results from the mean change from baseline analysis are provided in the table below, where only at 6 out of 16 timepoints show a statistically significant difference between the Ganfort combination and bimatoprost, and a numerically lower value was not observed at all the rest of the timepoints.

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**Table** Study 192024-018T: Mean IOP (mm Hg) at Baseline and Mean Changes from Baseline at Each Scheduled Timepoint (ITT with LOCF)

| Timepoint | | Combination N = 261 | Bimatoprost N = 129 | Timolol N = 130 | Combination v. P-value | Combination v. P-value |
|---|---|---|---|---|---|---|
| Baseline | Hour 0 | 26.1 | 25.5 | 25.9 | 0.093 | 0.648 |
| | Hour 2 | 24.2 | 23.9 | 24.5 | 0.324 | 0.389 |
| | Hour 8 | 23.0 | 22.9 | 23.0 | 0.821 | 0.988 |
| Week 2 | Hour 0 | -9.2 | -7.8[a] | -7.0[b] | < 0.001 | < 0.001 |
| | Hour 2 | -8.0 | -7.1[a] | -6.2[b] | 0.026 | < 0.001 |
| | Hour | -7.4 | -6.1[a] | -5.1[b] | < 0.001 | < 0.001 |
| Week 6 | Hour | -9.5 | -8.5[a] | -7.0[b] | 0.005 | < 0.001 |
| | Hour | -7.9 | -7.5 | -6.4[b] | 0.237 | < 0.001 |
| | Hour | -7.5 | -6.5[a] | -5.2[b] | 0.011 | < 0.001 |
| Month 3 | Hour | -9.1 | -8.5 | -7.0[b] | 0.067 | < 0.001 |
| | Hour | -7.6 | -7.7 | -6.2[b] | 0.809 | < 0.001 |
| | Hour | -7.1 | -6.2[a] | -5.0[b] | 0.030 | < 0.001 |
| Month 6 | Hour | -8.4 | -7.9 | -7.0[b] | 0.143 | < 0.001 |
| | Hour | -7.2 | -7.3 | -6.4[b] | 0.861 | 0.038 |
| | Hour | -7.0 | -6.4 | -4.9[b] | 0.200 | < 0.001 |
| Month 9 | Hour | -8.6 | -8.0 | -6.6[b] | 0.088 | < 0.001 |
| | Hour | -7.1 | -7.2 | -6.0[b] | 0.751 | 0.007 |
| Month 12 | Hour | -8.4 | -7.8 | -6.7[b] | 0.063 | < 0.001 |
| | Hour | -7.0 | -7.2 | -6.0[b] | 0.668 | 0.006 |

Source: Section 5.3.5.1, Report 109204-018T, Tables 14.2-1.1 and 14.2-3.1 to 14.2-3.6, M5, vol 4.

N = Number of randomised patients.

a  Ganfort combination mean decrease from baseline in IOP statistically significantly greater than Bimatoprost ($p \leq 0.030$).

b  Ganfort combination mean decrease from baseline in IOP statistically significantly greater than Timolol ($p \leq 0.038$).

A statistically significant difference in favour of the Ganfort combination towards bimatoprost in monotherapy was not found in this population.

**192024-021T**

At one point only, was the difference between the bimatoprost 0.03 %/timolol 0.5 % ophthalmic solution combination and bimatoprost 0.03 % ophthalmic solution in mean change from baseline, statistically

significant. The difference between the Ganfort combination and timolol 0.5 % ophthalmic solution was statistically significant at all timepoints but one.

**Study 192024-021T:** Mean IOP (mm Hg) at Baseline and Mean Changes from Baseline at Each Scheduled Timepoint (ITT with LOCF)

| Timepoint | | Combination N = 272 | Bimatoprost N = 136 | Timolol N = 133 | Combination v. Bimatoprost P-value | Combination v. P-value |
|---|---|---|---|---|---|---|
| Baseline | Hour 0 | 25.8 | 26.1 | 26.5 | 0.356 | 0.054 |
| | Hour | 24.5 | 25.1 | 25.1 | 0.102 | 0.123 |
| | Hour | 23.6 | 23.8 | 23.7 | 0.583 | 0.973 |
| Week 2 | Hour | -9.4 | -8.8 | -7.8[a] | 0.091 | < 0.001 |
| | Hour | -8.3 | -8.3 | -6.9[a] | 0.967 | < 0.001 |
| | Hour | -7.9 | -7.2 | -5.8[a] | 0.136 | < 0.001 |
| Week 6 | Hour | -9.6 | -9.0 | -7.7[a] | 0.093 | < 0.001 |
| | Hour | -8.1 | -8.5 | -6.9[a] | 0.294 | 0.003 |
| | Hour | -7.9 | -7.4 | -5.3[a] | 0.225 | < 0.001 |
| Month 3 | Hour | -9.2 | -8.9 | -7.6[a] | 0.388 | < 0.001 |
| | Hour | -8.0 | -8.6 | -7.1[a] | 0.175 | 0.022 |
| | Hour | -7.7 | -7.2 | -5.5[a] | 0.328 | < 0.001 |
| Month 6 | Hour | -8.6 | -8.6 | -7.2[a] | 0.890 | < 0.001 |
| | Hour | -7.5 | -8.3[b] | -6.8[a] | 0.047 | 0.050 |
| | Hour | -7.3 | -7.1 | -5.4[a] | 0.594 | < 0.001 |
| Month 9 | Hour | -8.4 | -8.0 | -6.9[a] | 0.340 | 0.001 |
| | Hour | -7.2 | -7.9 | -6.5 | 0.068 | 0.071 |
| Month 12 | Hour | -8.1 | -7.8 | -6.7[a] | 0.435 | < 0.001 |
| | Hour | -7.2 | -7.7 | -6.3[a] | 0.184 | 0.026 |

Source: Section 5.3.5.1, Report 109204-021T, Tables 14.2-1.1 and 14.2–3.1 to 14.2-3.6, M5 vol 11.

a   Ganfort combination mean decrease from baseline in IOP statistically significantly greater than Timolol (p ≤ 0.050).

b   Bimatoprost mean decrease from baseline in IOP statistically significantly greater than the Ganfort combination (p = 0.047).

The difference between the combination and bimatoprost in mean change from baseline was statistically significant only at one point. The difference between the combination and timolol was statistically significant at all timepoints except 2.

Results for an important secondary parameter are shown in the table below.

**Study 192024-021T:** Number (%) of Patients Achieving a Target IOP < 18 mm Hg at all Follow-up Timepoints (ITT population)

| Achieved IOP < 18 mm Hg[a] | Combination N = 272 | Bimatoprost N = 136 | Timolol N = 133 |
|---|---|---|---|
| Unadjusted | 65 (23.9%) | 27 (19.9%) | 12 (9.0%)[b] |
| Adjusted | 182 (66.9%) | 81 (59.6%) | 60 (45.1%)[b] |

Source: Section 5.3.5.1, Report 192024-021T, Tables 14.2-5 and 14.2-6, M5 vol 11

Note: IOP measured at all follow-up timepoints. Adjusted IOP = IOP measurement adjusted for corneal thickness using Ehlers' approach.

a    Scheduled follow-up IOP measurements were at Hours 0, 2, and 8 at Weeks 2 and 6 and Months 3 and 6 and Hours 0 and 2 at Months 9 and 12.

b    Ganfort combination patients achieving IOP < 18 mm Hg statistically significantly higher than Timolol (p < 0.001).

**192024-504T**

A statistically and clinically significant decrease in mean diurnal IOP was found in all groups at all visits (p<0.001). The mean difference between the Ganfort combination and bimatoprost was not statistically significant at any time point, but the decrease from baseline was numerically larger at all timepoints with the combination. The difference between the Ganfort combination and timolol was statistically in favour of the combination at all timepoints.

**Study 192024-504T:** Baseline and Mean Changes from Baseline in Diurnal IOP (mm Hg) at Each Scheduled Visit (ITT with LOCF)

| Timepoint | Within-group Comparison | | | Combination versus Bimatoprost[a] | | Combination versus Timolol[a] | |
|---|---|---|---|---|---|---|---|
| | Combination N = 155 | Bimatoprost N = 148 | Timolol N = 155 | Mean difference | P-value (95% CI) | Mean difference | P-value (95% CI) |
| Baseline | 27.36 | 26.97 | 27.19 | 0.33 | 0.294 | 0.19 | 0.541 |
| Week 2 | -9.21 | -9.19 | -7.33 | 0.05 | 0.888 | -1.99 | < 0.001 |
| Week 6 | -9.56 | -9.48 | -7.35 | 0.02 | 0.962 | -2.19 | < 0.001 |
| Week 12 | -9.77 | -9.71 | -7.60 | 0.03 | 0.941 | -2.17 | < 0.001 |

Note: Diurnal IOP was calculated by the mean of Hour 0, 2 and 8 IOP values

a  A negative difference between the 2 treatment groups indicates that the mean change was in favour of the Ganfort combination group

Secondary endpoints:

For the percentage of patients achieving IOP < 18 mm Hg at all timepoints, the figures were 18.7 %, 20.9 %, and 5.2 % in the combination group, the bimatoprost, and the timolol group, respectively, with the latter difference being statistically significant.

The percentage of patients with a decrease in IOP from baseline of > 20 % at all timepoints was also similar between the Ganfort combination and the bimatoprost group and statistically significantly higher than in the timolol group with 62.6 %, 59.5 %, and 36.8 % achieving this endpoint, respectively.

For the decrease of the mean diurnal IOP > 20 % at all visits, the figures were 83.9 %, 87.2 %, and 60.0 % in the 3 groups, respectively.

This study failed to show a statistically significant difference in IOP-lowering between the Ganfort combination and bimatoprost in this population of patients with an inadequate response to beta-blockers.

**192024-026T**
In this study, the requirements for non-inferiority of the Ganfort combination compared to the concurrent use of the single agents was that the difference between the mean IOP in the combination group and in the concurrent group should not only be less than 1.5 mm Hg at the 3 timepoints, but also less than 1.0 mm Hg for at least 2 of the 3 timepoints.

For the mean IOP at each time point at week 3, the difference in mean IOP was within the 1.0 mm Hg non-inferiority margin at one observation, namely at H8, and within the 1.5 mm Hg margin at all 3 timepoints. The upper limit of the 95 % confidence interval for the between group difference was 1.28 mm Hg, 1.29 mm Hg, and 0.51 mm Hg at hours 0, 2 and 8, respectively, at week 3. The differences in mean IOP between the Ganfort combination and the concurrent groups were -0.15 to 0.61 mm Hg. However it is noted that in this treatment naïve population, a statistically significant difference between the combination and the bimatoprost group was observed.

**Study 192024-026T:** Mean IOP (mm Hg) at Each Scheduled Timepoint (ITT with LOCF)

| Timepoint | | Combination N = 178 | Concurrent N = 177 | Bimatoprost N = 90 | Combination vs Concurrent P-value Difference (95% CI) | Combination vs Bimatoprost P-value Difference (95% CI) | Concurrent vs Bimatoprost P-value Difference (95% CI) |
|---|---|---|---|---|---|---|---|
| Baseline | Hour 0 | 26.2 | 26.4 | 26.2 | 0.410 -0.18 (-0.62, 0.25) | 0.923 -0.03 (-0.56, 0.50) | 0.562 0.16 (-0.38, 0.69) |
| | Hour 2 | 24.9 | 25.2 | 25.1 | 0.300 -0.29 (-0.83, 0.26) | 0.530 -0.21 (-0.86, 0.45) | 0.821 0.08 (-0.58, 0.73) |
| | Hour 8 | 23.7 | 23.9 | 23.8 | 0.400 -0.26 (-0.85, 0.34) | 0.466 -0.27 (-0.99, 0.45) | 0.973 -0.01 (-0.74, 0.71) |
| Week 3 | Hour 0 | 16.5 | 15.8 | 17.7 | 0.084 0.60 (-0.08, 1.28) | 0.007 -1.15 (-1.97, -0.32) | < 0.001 -1.75 (-2.58, -0.92) |
| | Hour 2 | 16.2 | 15.5 | 16.8 | 0.077 0.61 (-0.07, 1.29) | 0.216 -0.52 (-1.34, 0.30) | 0.008 -1.13 (-1.96, -0.30) |
| | Hour 8 | 15.4 | 15.5 | 16.8 | 0.663 -0.15 (-0.80, 0.51) | 0.001 -1.32 (-2.12, -0.52) | 0.004 -1.17 (-1.97, -0.38) |

Source: Section 5.3.5.1, Report 192024-026T, Tables 14.2-1.1 and 14.2-1.2, M5, vol 26

Strictly, the non-inferiority criteria were not fulfilled, as the non-inferiority margin of 1.0 mm Hg was met at only one and not at two timepoints, as requested. However, this demand is ambitious as usually the 1.5 mm Hg is applied as limit for non-inferiority.

The PP-results confirmed the ITT results.

Secondary endpoints:
At week 3, the mean diurnal IOP was 16.1 mm Hg, 15.6 mm Hg, and 17.1 mm Hg in the Ganfort combination group, the concurrent group, and the bimatoprost group, respectively. (p= 0.222 for the Ganfort combination vs. concurrent group).

*Ancillary analyses*
No ancillary analyses have been performed.

- Analysis performed across trials (pooled analyses)

The applicant provided responder analyses, which included analyses based on diurnal IOP from the pooled studies 192024 018T & 021T. Since the design of the two studies 192024-018T and -021T were identical (except for the choice of primary efficacy parameter), a pooled analysis was considered to be justified.

Two analyses were presented, namely percentage of patients achieving greater than 20% decrease from baseline diurnal IOP at all visits and the percentage achieving an IOP below 18 mmHg at all follow-up timepoints. In both cases, analyses were performed for the overall population and patients who were uncontrolled by prostamide/prostaglandins. There is a statistically significant benefit of the Ganfort combination vs. bimatoprost monotherapy. The results provided are summarized below:

Percentage of patients achieving greater than 20% decrease from baseline diurnal IOP at all visits
The results provided by the applicant show that a decrease greater than 20% from baseline diurnal IOP is seen in a similar percentage comparing the overall population (68.1%, 1061 patients) vs. patients previously treated with prostamide/prostaglandins (67.9%, 373 patients). In both cases the results obtained with the fixed Ganfort combination are statistically significantly superior compared to those obtained with bimatoprost monotherapy (58.1% overall, 48.9% prostamide/prostaglandin patients).


Table **Pooled 192024-018T & -021T: Incidence of patients achieving >20% decrease from baseline diurnal IOP at all visits**

| Study Population | Total patient # | Ganfort® | Bimatoprost | Timolol |
|---|---|---|---|---|
| Overall* | 1061 | 68.1% | 58.1%[a] | 38.0% |
| Prostaglandin/prostamide wash-out** | 373 | 67.9% | 48.9%[b] | 31.5% |

*Section 5.3.5.3 Pooled Efficacy   Table 2.7.3.13-10 M5, vol 29 (Page 39)
** Section 2.7.3.6.1  Table 99.3 M2, vol 2 (Page 51)
[a] p = 0.003   [b] p = 0.001


Percentage of patients achieving an IOP below 18 mmHg at all Follow-up timepoints
The applicant establishes that a similar percentage of responders has been obtained after treatment with the Ganfort combination (23.3% Overall population; 18.7% patients previously treated with prostamide/prostaglandins) and these percentages are superior to those obtained with bimatoprost monotherapy (18.1% and 10.2% respectively).

The incidence of patients achieving the target IOP of < 18 mm Hg at all follow-up timepoints is summarised for the pooled populations in the following Table.

Table    **Pooled    192024-018T    &    -021T:    Incidence    of    patients    achieving IOPs < 18 mm Hg at all follow-up timepoints**

| Study Population | Total patient # | Ganfort® (patient #) | Bimatoprost (patient #) | Timolol (patient #) |
|---|---|---|---|---|
| Overall* | 1061 | 23.3% (124/533) | 18.1%[c] (48/265) | 8.0% (21/263) |
| Prostaglandin/prostamide wash-out** | 373 | 18.7% (36/193) | 10.2%[d] (9/88) | 8.7% (8/92) |

*Section 5.3.5.3 Pooled Efficacy   Table 2.7.3.13-8 M5, vol 29 (Page 37)

** Section 2.7.3.6.1  Table 98.3 M2, vol 2 (Page 48)

[c] p = 0.058    [d] p = 0.027

In the target IOP analysis for the pooled Studies 192024-018T/-021T, an unadjusted IOP < 18 mm Hg was achieved at all timepoints by statistically significantly more patients in the Ganfort combination group (18.7%) compared with the Bimatoprost group (10.2%; p = 0.027) and Timolol group (8.7%; p = 0.043).

The proportion of patients who achieved IOPs < 18 mm Hg at all follow-up timepoints in the subpopulation of patients receiving prostaglandins/prostamides was comparable to the results for the whole population.

A statistically significant difference in favour of the Ganfort combination compared to both bimatoprost and timolol was noted for the proportion of patients who achieved IOP<18 mm Hg in the subpopulation of patients who were not satisfactorily controlled on prostaglandin/prostamide alone. This result is in contrast to the similarity of the mean IOP values in the subpopulation and the total population.

The use of these responder analyses is consistent with recent scientific and clinical recommendations.

The applicant has also provided an additional analysis of the pooled 192024-018T and -021T studies, which demonstrates a statistically significant better effect in the treatment-naïve patients. This might be an indirect reflection of the clinical experience, that the effect of the treatment with timolol decreases with extended use.

- Clinical studies in special populations

No studies in special populations have been conducted.

- Supportive studies

No supportive studies have been submitted.

- Discussion on clinical efficacy

None of the superiority trials showed a consistent statistically significant difference between the Ganfort combination and bimatoprost in change from baseline IOP. In contrast, a statistically superior effect was observed for the Ganfort combination over timolol. Taking into account strictly the protocol defined primary endpoints, the pivotal studies could  be considered to have failed.

However, scientifically and clinically approved recent literature[1] state that the relevant aims of anti-glaucoma/IOP-decreasing therapy are a diurnal IOP < 18 mm Hg and a reduction of > 20 % in IOP from baseline. In the responder analyses provided these goals have been achieved, with a statistically and clinically significant margin between the Ganfort combination product and bimatoprost (Lumigan) monotherapy in patients with glaucoma or ocular hypertension.

Additionally, the applicant has also analysed the subgroup of patients who was insufficiently controlled on prostaglandin/prostamide, regarding the generally accepted responder analyses, i.e. the percentage of patients achieving IOP control < 18 mm Hg and the percentage of patients with > 20 % reduction of diurnal IOP from baseline. The subpopulation encompasses around one third of the study population, namely 373/1061 patients.  The difference in the incidence of patients achieving >20 % decrease in diurnal IOP from baseline is clinically and statistically significant between the bimatoprost/timolol combination group and the bimatoprost group. For the analysis in the incidence of patients achieving IOP < 18 mm Hg at all follow-up visits, the difference between the combination and the monotherapy group is statistically significant in the analysed subpopulation and clearly numerically different in the overall population.

Thus, results from this important subpopulation support a better effect of the Ganfort combination therapy than of bimatoprost alone. Considering the results of Study 192024-504T that addresses only patients not responsive to β-blocker therapy the full picture of efficacy in the proposed therapeutic indication seems justified.

Study 192024-504T specifically evaluated the effect of the Ganfort combination in patients not adequately controlled with beta-blockers. Although clear evidence of superiority of the combination over timolol monotherapy was shown in this study, a statistical superiority vs. bimatoprost has not been proved.

With regards to study 192024-026T and according to the applicant´s margin of non-inferiority, this study has not proved the non-inferiority of the Ganfort combination (Bimatoprost 0.03%/Timolol 0.5%) versus the concurrent administration of both drugs in treatment-naïve patients. The upper limit of the 95 % confidence interval for the between group difference in mean IOP was less than 1.0 mmHg at hour 8 (one timepoint instead the two proposed in the protocol) but less than 1.5 mmHg at all timepoints. However, it should be highlighted that the margin of non-inferiority of 1.5 mmHg could be considered acceptable to prove non-inferiority.

Concerns regarding the appropriateness of comparing the bimatoprost monotherapy evening dosing with the bimatoprost/timolol combination morning dosing have subsequently been addressed with reference to the initial investigations with bimatoprost dosing regimen, which showed comparable results regardless of morning or evening dosing. The accepted timolol 0.5 % morning dose regimen has been shown to be optimal, to manage the physiological diurnal variation with the morning IOP peak. The proposed morning posology with the bimatoprost/timolol combination as stated in section 4.2 of the SPC is therefore justified. An adequate explanation has been also been added in section 5.1 of the SPC, where it states that evening dosing may be considered if necessary for patient compliance.

The Ocular Hypertension Treatment Study (OHTS) recently reported that corneal thickness was a very significant predictor of progression to glaucoma even after adjusting for other known risk factors (Gordon 2002).  The authors concluded that corneal thickness must be considered, not only to improve the classification of patients with respect to the risk of progression to vision loss, but also to better define a patient's response to therapy. The applicant highlights that the inclusion of such adjusted analyses in most of the variables are provided as supplementary information.

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[1] 1. European Glaucoma Society Terminology and Guidelines for glaucoma 2nd ed. 2003
   2. AGIS Investigators.  The Advanced Glaucoma Intervention Study (AGIS): 7.
   3. The relationship between control of intraocular pressure and visual field deterioration.  Am J Ophthalmol 2000; 130:429-440)

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In conclusion, the presented studies in connection with the submitted response to the CHMP list of Questions seem to justify the therapeutic indication and posology for the fixed combination of bimatoprost 0.03 % and timolol 0.5 %: reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

**Clinical safety**

- Patient exposure

Patient exposure

The database contains safety information of 1974 subjects, of whom 18 were healthy volunteers. A number of 861 patients received the bimatoprost 0.03 %/timolol 0.5 % combination, 468 patients hereof were exposed for 12 months.

**Table**         **Number of Subjects Exposed to Combination and Comparators**

| Study Number | Duration of Therapy | Number of Subjects | | Number of Subjects Evaluable for Safety[a] in Each Treatment Arm | | | |
|---|---|---|---|---|---|---|---|
| | | Enrolled[a] | Evaluable for Safety[b] | Combination | Bimatoprost | Timolol | Concurrent (Bimatoprost and Timolol) |
| Combination vs monotherapy | | | | | | | |
| 192024-018T | 12 months[c] | 520 | 520 | 261 | 129 | 130 | NA |
| 192024-021T | 12 months[c] | 541 | 541 | 272 | 136 | 133 | NA |
| *Pooled* | | *1061* | *1061* | *533* | *265* | *263* | *NA* |
| 192024-504T | 12 weeks | 458[d] | 453[e] | 152 | 147 | 154 | NA |
| Combination vs concurrent therapy | | | | | | | |
| 192024-026T | 3 weeks | 445 | 442 | 176 | 90 | NA | 176 |
| **Phase III total** | | *1964* | *1956* | *861* | *502* | *417* | *176* |
| Combination vs monotherapy in healthy subjects | | | | | | | |
| 192024-503T | 3 x 7 days[f] | 18 | 18 | 18[f] | 17[e] | 17[f] | NA |
| All studies | | | | | | | |
| **Overall total** | | **1982** | **1974** | **879** | **519** | **434** | **176** |

a   Allocated to receive study treatment

b   Subjects that were enrolled in studies and received a dose of study medication (safety population)

c   After an initial 3-month period, patients entered a 9-month masked extension phase

d   A total of 459 patients were enrolled but due to misconduct identified at an investigator site, the single patient ( Timolol group) recruited at this site, was excluded from all analyses before database lock

e   In study 192024-504T, 2 patients in the Ganfort combination group and 1 each in the Bimatoprost and Timolol groups recruited at one investigator site were excluded from safety analyses after receiving the wrong study treatment at week 6; in addition, one patient in the Ganfort combination group discontinued the study without receiving study medication, and was, therefore, excluded from the safety population

f   Subjects were dosed sequentially for 7 days with each of the 3 treatments with a 1-week washout between treatments.

The magnitude and duration of the exposure to the study drug is satisfactory for the drug intended for long-term therapy.

Demographic information (all studies): The patients' age ranged from 18 to 91 years with the preponderance of patients from 45-65 years (54 %) and with 38 % being ≥ 65 years.  The male to female gender ratio was 45.5:55.5. The majority (79 %) of patients were Caucasian and 13 % were black.

The demographic distribution in the study population is unremarkable. The following types of glaucoma were represented in the study population: primary open angle glaucoma, pigmentary glaucoma, pseudoexfoliative glaucoma and residual (patent iridotomy).

As for diagnosis, the population in the clinical studies differed with a clear preponderance of glaucoma patients in the 192024-504T study as compared to the more evenly distribution between glaucoma and ocular hypertension in the 192024-018T and 192024-021T trials and an opposite distribution in the 192024-026T study.

- Adverse events
An appropriate battery of predefined safety parameters encompassing the adverse events, blood pressure, heart rate, visual acuity, biomicroscopy, ophthalmoscopy, visual field examination, cup/disc ratio, pregnancy testing, blood chemistry, haematology, and urine analysis were investigated.

Overall, the most frequently reported adverse events in the patients were conjunctival hyperaemia, growth of eye lashes, burning sensation in the eye, eye pruritus, infection (body as a whole), superficial punctuate keratitis, and cataract for the Ganfort combination group.

A summary of adverse events in the 4 Phase III studies is shown in the table below.

**Table** **Summary of Adverse Events (All Phase III Studies)**

| Number of patients (%) | Study 192024-504T | | | Pooled 192024-018T/021T 3 month data | | | Pooled 192024-018T/021T 12 month data | | | Study 192024-026T | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Comb N = 152 | Bimat N = 147 | Timolol N = 154 | Comb N = 533 | Bimat N = 265 | Timolol N = 263 | Comb N = 533 | Bimat N = 265 | Timolol N = 263 | Comb N = 176 | Concurr N = 176 | Bimat N = 90 |
| All AEs | 86 (56.6) | 83 (56.5) | 44 (28.6)[a] | 316 (59.3) | 173 (65.3) | 126 (47.9)[a] | 418 (78.4) | 218 (82.3) | 189 (71.9)[a] | 71 (40.3) | 82 (46.6) | 43 (47.8) |
| ocular | 79 (52.0) | 76 (51.7) | 27 (17.5)[a] | 247 (46.3) | 143 (54.0) | 85 (32.3)[a] | 323 (60.6) | 181 (68.3)[b] | 123 (46.8)[a] | 66 (37.5) | 76 (43.2) | 37 (41.1) |
| non-ocular | 18 (11.8) | 22 (15.0) | 19 (12.3) | 13 (25.0) | 69 (26.0) | 68 (25.9) | 264 (49.5) | 139 (52.5) | 139 (52.9) | 13 (7.4) | 20 (11.4) | 14 (15.6) |
| Treatment-related AEs | 73 (48.0) | 72 (49.0) | 23 (14.9)[a] | 221 (41.5) | 135 (50.9) | 65 (24.7)[a] | 256 (48.0) | 159 (60.0)[b] | 83 (31.6)[a] | 62 (35.2) | 74 (42.0) | 34 (37.8) |
| SAEs | 0 | 1 (0.7) | 1 (0.6) | 6 (1.1) | 2 (0.8) | 5 (1.9) | 36 (6.8) | 15 (5.7) | 16 (6.1) | 0 | 0 | 0 |
| Treatment-related SAEs | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 | 0 | 0 | 0 | 2 (0.4) | 1 (0.4) | 1 (0.4) | 0 | 0 | 0 |
| Withdrawal due to AEs | 7 (4.6) | 3 (2.0) | 2 (1.3) | 21 (3.9) | 18 (6.8) | 4 (1.5) | 37 (6.9) | 26 (9.8) | 9 (3.4)[a] | 3 (1.7) | 3 (1.7) | 1 (1.1) |

Source: Section 5.3.5.1, Reports 192024-504T, Tables 14.3-4, 14.3-11 and 14.3-14 M1, vol. 9 and 192024-026T, Tables 14.3-4, 14.3-11 and 14.3-13 M1, vol. 9 ; Section 2.7.4.7, 3-month Pooled Tables for Studies 192024-018T/-021T, Table 2.5.5.17-4 M1, vol. 9 ; Section 5.3.5.3, 12-month Pooled Tables for Studies 192024-018T/021T, Table 2.7.4.17-4 M1, vol. 9

Note: Comb = Combination; Bimat = Bimatoprost; Concurr = Concurrent Bimatoprost/Timolol

a Combination incidence of AEs statistically significantly higher than Timolol (p ≤ 0.041)

b Combination incidence of AEs statistically significantly lower than Bimatoprost (p ≤ 0.043)

The applicant hypothesizes that the observed less frequent adverse events in the Ganfort combination group, conjunctival hyperaemia, could be explained by a beta-blocker inhibition of nitric oxide production. This latter compound mediates the vasodilatation characteristic for bimatoprost (and other prostaglandin-like ocular drugs). For the pooled studies 192024-018T and -021T, overall statistically significant fewer treatment related adverse were reported for the Ganfort combination than the bimatoprost group with 48 % and 60 %. For timolol the figure was 32 %.

For a few adverse events, however, like burning sensation, superficial keratitis, FB sensation and erosion, the frequency was numerically higher in the Ganfort combination group than in the bimatoprost group.

The incidence of the potentially concerning ocular adverse events for prostaglandin analogues, i.e. iritis, uveitis, increased iris pigmentation cystoid macular oedema is similar to what has earlier been reported with Lumigan; with 1 case of uveitis and 4 cases of iritis and 1 case of increased iris pigmentation recorded in the Ganfort combination group across all studies.

The company was asked to justify why they considered the 3-month safety data from the pooled analysis to be similar to the safety data from -504T. The apparent discrepancies were in the incidence of eye pruritus (5.1% vs. 3.9%), superficial punctuate keratitis (3.4% vs. 0%), eye dryness (3.0% vs. 0.7%). These adverse events all fell within the same frequency category in terms of presentation of the SPC Point 4.8 Undesirable effects and are grossly similar. Therefore, it was considered appropriate to use the data from the 12-month pooled analysis to support the undesirable effects section of the SPC.

For the ophthalmological safety evaluation of specific relevance for a glaucoma population, no unexpected findings were made for visual acuity, cup/disc ratio or visual field. Neither for laboratory findings nor vital signs were noteworthy observations made.

Overall, more treatment related adverse events were reported for the bimatoprost group than for the Ganfort combination group. Nevertheless the following adverse events were reported at >10% during clinical trials with the Ganfort combination: conjunctival hyperaemia and eyelash growth.

- Serious adverse event/deaths/other significant events

A total of 4 deaths were reported in the study programme. All were regarded as not treatment related. The reports included 2 myocardial infarctions in the bimatoprost and the timolol group, respectively, a cerebrovascular disorder, and death following injuries after a car accident both in the Ganfort combination group, all occurring in the 12-month studies. These findings are not surprising considering the composition of the population.

- Laboratory findings/Vital signs

No new concerns were raised with the results from laboratory analyses. No major clinically significant differences in heart rate or blood pressure between the treatment groups were reported.

- Safety in special populations

Studies in special populations were not conducted

- Safety related to drug-drug interactions and other interactions

No studies to investigate possible interactions with other topical medication were carried out.

- Discontinuation due to adverse events

The most common adverse events leading to discontinuation in the Ganfort combination group were conjunctival hyperaemia (1.5%), photophobia (0.6%) and iritis (0.6%). The overall discontinuation rate because of adverse events was statistically significantly lower with the fixed Ganfort combination than with the bimatoprost monotherapy regimen, namely 3.6 % versus 7.9 % (p=0.008) respectively.

Overall, the discontinuation rate because of adverse events was not high.

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- Post marketing experience

Post-marketing experience with the fixed dose combination Ganfort is not available.

- Discussion on clinical safety

Overall, the safety pattern of the bimatoprost / timolol combination is consistent with that of the well-known active constituents. However, some of the specific bimatoprost adverse events like conjunctival hyperaemia, eyelash growth and ocular pruritus were less frequent with the Ganfort combination than with bimatoprost alone.

The discontinuation rate because of adverse events was statistically significantly lower with the fixed Ganfort combination than with the bimatoprost monotherapy regimen, namely 3.6 % versus 7.9 % (p=0.008).

Overall, the adverse event pattern or frequency of the Ganfort combination is not concerning, in particular a low frequency for the typical adverse events for the class: inflammation, and changes of iris pigmentation is noted.

The long-term safety population evaluated under controlled conditions is considered sufficient to assess a favourable safety profile for the Ganfort combination. The MAH has addressed the posed questions: the omission of flare meter investigations has been justified, the presentation and interpretation of the adverse events frequency reporting has been explained and justified, and the low incidence of iris pigmentation has been adequately discussed. Hence, no outstanding safety issues remain.

## 1.5 Pharmacovigilance

### Description of the Pharmacovigilance system

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

When the necessary changes to the forwarded document have been implemented by the applicant, this will be communicated to the EMEA.

### Risk Management Plan

The two active substances in Ganfort eye drops are bimatoprost and timolol, which have been available on the market for more than 5 years and more than 20 years in ocular formulations, respectively. The systemic absorption of both compounds is minimal. The safety will be monitored with the Pharmacovigilance system implemented by the applicant and will be reviewed in the PSURs. The argumentation put forward by the applicant for not submitting a risk management plan was considered to be acceptable by the CHMP.

## 1.6 Overall conclusions, risk/benefit assessment and recommendation

### Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### Non-clinical pharmacology and toxicology

Ganfort consists of a combination of two well-known ophthalmic drugs, timolol (0.5% or 5 mg/mL) and bimatoprost (0.03% or 0.3 mg/mL). The rationale for the fixed combination is well established.

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The metabolism of bimatoprost and timolol differ and are therefore not expected to affect or alter one another. Since bimatoprost and timolol act through different receptors it is unlikely that interaction would occur at the receptor level.

The key findings following six months of repeated dosing of monkeys included increased iridial pigmentation in the bimatoprost and Ganfort treatment groups. The increased iridial pigmentation caused by bimatoprost may be an irreversible effect observed in both monkey and humans after long treatment periods. Bimatoprost and timolol reveal no hazard for humans with respect to genotoxicity or carcinogenic potential. The use of Ganfort is not recommended during pregnancy. Ganfort is unlikely to pose a risk to the environment.

**Efficacy**
Overall, the study population and the chosen efficacy end points were appropriate. The timing of dosing for the Ganfort combination and the bimatoprost groups differed. However this has been justified with reference to the initial investigations with the bimatoprost dosing regimen, which showed comparable results regardless of morning or evening dosing.

A consistent statistically significant difference between the bimatoprost 0.03 %/timolol 0.5 % combination and bimatoprost 0.03 % was not consistently seen in any of the superiority trials for the chosen primary endpoint.

The applicant has however provided a responder analysis addressing the scientifically and clinically accepted important parameters, namely the percentage of patients achieving an IOP control < 18 mm Hg at all timepoints and a decrease in diurnal IOP from baseline > 20 % at all visits. These analyses were performed for the overall population and the subpopulation of patients inadequately controlled on prostaglandins/prostamides. This subpopulation encompasses around one third of the study population, namely 373/1061 patients. The difference in the incidence of patients achieving >20 % decrease in diurnal IOP from baseline is clinically and statistically significantly superior in favour of the bimatoprost/timolol combination group versus the bimatoprost group for both populations. As for the analysis in the incidence of patients achieving IOP < 18 mm Hg at all follow-up visits the difference between the Ganfort combination and the monotherapy group is statistically significant in the analysed subpopulation and clearly numerically different in the overall population in favour of the Ganfort combination.

Thus, results from this important subpopulation of patients inadequately controlled on prostaglandins/prostamides support a better effect of the Ganfort combination therapy than of bimatoprost alone. Considering the results of study 192024-504T that addresses only patients not responsive to β-blocker therapy, the full picture of efficacy in the proposed therapeutic indication seems justified, in view of the better safety profile, which is primarily reflected in a lower frequency of adverse reactions and a lower withdrawal rate because of adverse events.

In the non-inferiority study against the concurrent regimen, proof of non-inferiority was not found obeying all the predefined criteria, which were, admittedly, demanding. The achieved differences, however, were within the standard criteria for non-inferiority of 1.5 mm Hg.

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

- User consultation
  The applicant has provided detailed results of readability testing performed according to the European Commission Guideline on Packaging Information of Medicinal Products for Human Use Authorised by the Community and as per the guidance provided by the EC "Guideline on the readability of the label and package leaflet (PL) of medicinal products for human use"

The Package Leaflet fully conforms to the standards set. The applicant has performed readability testing according to the "readability guideline" and has subsequently taken appropriate measures to improve the readability.

**Risk-benefit assessment**

Four clinical randomised, double-masked, parallel studies have been conducted to evaluate the efficacy and safety of the bimatoprost 0.03 /timolol 0.5 % combination ophthalmic solution in patients with open angle glaucoma or ocular hypertension.

Two 12-months <u>superiority</u> studies of similar design compared the Ganfort combination with the individual components applied as monotherapy. The Ganfort combination was also compared to each monotherapy in a <u>superiority</u> study of 12 weeks duration.

A <u>non-inferiority</u> study compared the Ganfort combination with the adjunctive application of bimatoprost and timolol, and with bimatoprost monotherapy for internal validation, in a 3 weeks trial. The Ganfort combination was dosed once daily in the morning, bimatoprost was dosed once daily in the evening, and timolol was dosed twice daily (morning and evening with an interval of approximately 12 hours), consistent with the approved regimen.

Overall, the study population and the chosen efficacy end points were appropriate; however, the dosing regimen for the Ganfort combination and the bimatoprost groups differed. This has been justified with reference to the initial investigations with bimatoprost dosing regimen, which showed comparable results regardless of morning or evening dosing. The text regarding the dosing regimen in section 5.1 of the SPC adequately reflects this.

In none of the superiority trials was a consistent statistically significant difference between the Ganfort combination and bimatoprost seen for the chosen primary endpoint. The applicant has provided responder analyses addressing the scientifically and clinically accepted important parameters namely the percentage of patients achieving IOP control < 18 mm Hg, and a decrease in diurnal IOP from baseline > 20 %. These analyses were performed for the overall population and the subpopulation of patients inadequately controlled on prostaglandins/prostamides. This subpopulation encompasses around one third of the study population, namely 373/1061 patients. The difference in the incidence of patients achieving >20 % decrease in diurnal IOP from baseline is clinically and statistically significantly superior in favour of the bimatoprost/timolol combination group versus the bimatoprost group for both populations. As for the analysis in the incidence of patients achieving IOP < 18 mm Hg at all follow-up visits the difference between the Ganfort combination and the monotherapy group is statistically significant in the analysed subpopulation and clearly numerically different in the overall population in favour of the Ganfort combination.

Thus, results from this important subpopulation of patients inadequately controlled on prostaglandins/prostamides, support a better effect of the Ganfort combination therapy than of bimatoprost alone. Considering the results of study 192024-504T that addresses only patients not responsive to β-blocker therapy the full picture of efficacy in the proposed therapeutic indication is justified.

In study 504T a numerically superior effect was not found at all observation points. A statistically superior effect was observed for the Ganfort combination over timolol 0.5 %. In the non-inferiority study against the concurrent regimen, proof of non-inferiority was not found obeying the all the predefined criteria, which were, admittedly, demanding. The achieved differences were, however, within the standard criteria for non-inferiority of 1.5 mm Hg.

The long-term safety population evaluated under controlled conditions is considered sufficient to assess a favourable safety profile for the Ganfort combination.

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Upon request, the applicant has properly addressed the question why patients insufficiently responsive to timolol should switch to the fixed combination Ganfort instead of bimatoprost as monotherapy. It can be concluded that the population that is insufficiently controlled on β-blocker monotherapy, has been demonstrated to clearly respond to the bimatoprost/timolol combination with a once daily dosing regimen. The proportion of patients who reported at least one adverse reaction with the Ganfort combination was statistically significantly lower than with bimatoprost monotherapy, i.e. 48 % vs. 60 % (p=0.001). Likewise, the rate of discontinuation because of adverse events was 3.6 % in the Ganfort combination group as opposed to 7.9. % in the bimatoprost group (p= 0.008). These statistically significant differences are also clinically relevant and translate well to a presumed higher compliance in a clinical setting. Especially in a progressive disease without symptoms that are manifest to the patient, application of the medication in accordance with the ophthalmologist's prescription is a key point. Therefore, an enhanced compliance is of particular importance in the treatment of open-angle glaucoma or ocular hypertension.

The overall efficacy of the bimatoprost 0.03 %/timolol 0.5 % eye drops combination in the treatment of patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to β-blocker alone should be assessed in connection with the better safety profile, which is primarily reflected in a lower frequency of adverse reactions and a lower withdrawal rate because of adverse events.

Considering the arguments presented above a positive benefit-risk conclusion can be reached for the therapeutic indication: *Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.*

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of Ganfort in the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues was favourable and therefore recommended the granting of the marketing authorisation.