European Medicines Agency

London, 7 January 2010
Doc. Ref:EMA/105752/2010

ASSESSMENT REPORT
FOR
LUMIGAN

International Nonproprietary Name:
Bimatoprost

Procedure No. EMEA/H/C/391/X/0026

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

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1. Introduction

Lumigan has been given a Marketing Authorisation in the European Union since 8 March 2002 and is already available as 0.3 mg/ml eye drops, solution. This line extension concerns the addition of a new strength: Lumigan 0.1 mg/ml eye drops, solution

The indication applied for is the same as for the currently authorised Lumigan presentations: reduction of elevated intraocular pressure (IOP) in chronic open-angle glaucoma and ocular hypertension (as monotherapy or as adjunctive therapy to beta-blockers).

The new strength, Lumigan 0.1 mg/ml eye drops, solution was developed as an alternative to the currently authorised Lumigan 0.3 mg/ml eye drops, solution. Compared with the current authorised strength which contains 0.3 mg/ml bimatoprost and 50 ppm benzalkonium chloride, the new strength contains a third of the concentration of bimatoprost (0.1 mg/ml) and 200 ppm benzalkonium chloride. The higher concentration of benzalkonium chloride increases the ocular absorption of bimatoprost thus allowing for a lower concentration of bimatoprost to be administered (0.1 mg/ml). This new formulation, with a reduced concentration of bimatoprost, achieves comparable IOP-lowering efficacy to the current authorised strength and an improved overall safety profile.

2. Quality aspects

Introduction
The medicinal product Lumigan 0.1 mg/ml eye drops, solution is presented as a sterile, isotonic, colourless to slightly yellow solution. Each ml of solution contains 0.1 mg of the active substance bimatoprost. The other ingredients include: benzalkonium chloride, sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, hydrochloric acid or sodium hydroxide (to adjust pH) and purified water. Lumigan 0.1 mg/ml eye drops is a multidose eye drop formulation.

The solution is supplied in white opaque low density polyethylene bottles with polystyrene screw cap. Each bottle has a fill volume of 3 ml. Two pack sizes are available: cartons containing 1 or 3 bottles of 3 ml.

Active Substance
The active substance, bimatoprost, is a known active substance although there is no monograph for bimatoprost in the European Pharmacopoeia. The active substance used in the manufacturing of Lumigan 0.1 mg/ml eye drops is identical to the one used in the manufacturing of the currently authorized presentations: Lumigan 0.3 mg/ml eye drops, solution (EU/1/02/205/001-002). Therefore the applicant referred to the active substance information which was submitted for the already authorised presentation and confirmed that no changes have been made to the active substance.
With this line extension Allergan, the MAH for Lumigan re-submitted only the sections general information, manufacture, specification and batch analysis to facilitate the assessors' review. As no changes have been made to the information in these sections, this is considered acceptable.

Drug Product

- **Pharmaceutical Development**

The goal of the pharmaceutical development was to develop a lower strength than the currently authorised Lumigan 0.3 mg/ml eye drops, solution with an improved safety profile while maintaining the intra-ocular pressure lowering efficacy. A reduced exposure of the ocular surface to the active substance bimatoprost would yield superior safety and fewer ocular adverse events.

The developed formulation is the same as the currently authorised presentations, except for a lower bimatoprost concentration, increased benzalkonium chloride concentration, and decreased sodium chloride for isotonicity. The concentrations of the other excipients are the same as those used in the

already approved formulation of Lumigan. All excipients are both USP/NF and Ph Eur compendial grade materials where relevant pharmacopoeial monographs exist. Dibasic sodium phosphate heptahydrate has no Ph Eur compendial monograph and therefore the USP compendial monograph is used.

Compatibility with regard to excipients was established during drug product development of Lumigan 0.3mg/ml eye drop solution. As the same excipients are used, this justifies that no new data are presented.

Development studies were conducted to evaluate the ocular absorption of bimatoprost, stability of the formulation, compatibility with the container closure system, antimicrobial preservative effectiveness, and ocular tolerability. The study data concluded that 0.01% bimatoprost/200 ppm benzalkonium chloride ophthalmic solution is stable and well tolerated by the eyes.

- **Adventitious Agents**

No materials of animal and/or human origin are used in the medicinal product manufacturing process.

- **Manufacture of the Product**

One manufacturer is involved in the manufacturing of the finished product. The manufacturing process of the drug product is essentially the same as for the already authorised Lumigan eye drops and has been adequately described and presented in a flow chart. The used in-process controls are considered satisfactorily to guarantee an appropriate quality of the drug product. The critical manufacturing steps are identified and were validated.
Process validation data has been submitted on three batches. All batches meet the pre-defined finished product specifications and the data demonstrate reproducibility of the manufacturing process.

- **Product Specification**

Adequate finished product specifications have been set for this new presentation. The specifications include appropriate tests and acceptance criteria for physical appearance (clarity and colour), assay (bimatoprost and benzalkonium chloride), impurities, pH, osmolality, sterility, antimicrobial preservative effectiveness and particulate matter (visual). All analytical procedures used for testing the drug product have been properly described and all relevant methods have been satisfactorily validated in accordance with the EU/ICH Validation Guidelines. Certificates of analysis and adequate batch analysis data have been provided.

- **Stability of the Product**

The stability studies include long term and accelerated studies, a study under freeze/thaw cycling conditions and a photostability study. Finished product batches have been stored at 25ºC/40% RH (up to 18 months), at 30°C/65% RH (up to 18 months) and at 40ºC/25% RH (up to 6 months) in the proposed market packaging. Parameters investigated were: assay bimatoprost, related substances, assay BAK, physical appearance, pH, osmolality, sterility, antimicrobial preservative effectiveness, particulate matter, container leachables and water loss. The studies have been performed in accordance with the relevant stability testing guidelines.
The stability data were generated by validated, stability indicating methods and show satisfactory stability. Based on the stability data, the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The active substance used in the manufacture of Lumigan 0.1 mg/ml eye drops, solution is exactly the same as for the already authorized presentations.
The manufacturing process of the new formulation and excipients used are appropriate and well controlled. Appropriate finished product specifications have been set.
Batch analysis results show that the medicinal product can be reproducibility manufactured, compliant with the finished product specifications, and therefore the product should have a satisfactory and

uniform performance in clinic. Stability data show that the medicinal product is stable until the end of the proposed shelf life. At the time of the CHMP opinion, there were no unresolved quality issues.

2.1Overall conclusions, risk/benefit assessment and recommendation on Quality aspects

The new formulation has been adequately described. The excipients used in the preparation of the product and the manufacturing process selected are appropriate. The results of the tests indicate that the drug product can be reproducibility manufactured and therefore the product should have a satisfactory and uniform performance in clinic.

At the time of the CHMP opinion, there were no unresolved quality issues having an impact on the Benefit/Risk ratio of the product.

3. Non clinical aspects

Pharmacology

Bimatoprost is a synthetic prostamide, structurally analogue to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). It is made by replacement of the carboxylic acid group of $PGF_{2\alpha}$ with an electrochemically neutral substituent (an amide group). This is a critical change, since the carboxylic acid group is essential for interaction of $PGF_{2\alpha}$ with its target protein, termed the FP receptor. Bimatoprost and its close congeners appear to mimic the activity of a local hormone, prostamide $F_{2\alpha}$ ($PGF_{2\alpha}$ 1-ethanolamide), a substance that is biosynthetically derived from anandamide by a pathway that involves COX-2, but not COX-1.

The pharmacology of bimatoprost was extensively characterised by *in vitro* functional and radioligand binding studies. Results show an absence of meaningful interaction for bimatoprost with any of the known prostanoid receptors. In addition, bimatoprost and its congener have no meaningful interaction with cannabinoid receptors and over 100 drug receptor targets, ion channels, and transporters. Molecular, biological and pharmacological studies indicate that the bimatoprost-sensitive receptors are novel and may be classified as a new subtype.

Bimatoprost produced dose-related decreases in IOP of ocular normotensive dogs that were given doses ranging from 0.001% to 0.1%, once-daily for 5 days. In laser-induced ocular hypertensive cynomolgus monkeys, bimatoprost produced substantial decreases in IOP that ranged from -7 mm Hg to -16 mm Hg at the 0.001%, 0.01%, 0.03% and 0.1% single doses studied.

The mechanism of action with respect to lowering IOP has been studied in beagle dogs and cynomolgus monkeys. Bimatoprost 0.1% did not alter aqueous humour inflow in monkeys, according to fluorophotometric studies. Studies on total outflow facility in dogs and monkeys revealed no effect for bimatoprost on total outflow facility. In monkeys, direct measurement of uveoscleral outflow showed an increased uveoscleral outflow to bimatoprost. New evidence for the increases in uveoscleral and trabecular outflow were provided by results of organised remodelling of the uveoscleral outflow routes and morphological changes in the trabecular meshwork of cynomolgus monkeys following a long-term 1-year treatment with bimatoprost.

Bimatoprost appeared to be well-tolerated in animals with ocular surface hyperaemia as the only side effect observed in short-term pharmacological studies. Results of pharmacological and extensive safety evaluation studies suggest that the conjunctival hyperaemia associated with bimatoprost treatment results from non-inflammatory, pharmacologically based vasodilatation.

The pharmacology of bimatoprost does not appear to involve receptors associated with any known local hormone or neurotransmitter and, therefore, untoward interaction with other drugs is unlikely.

Pharmacokinetics

Study reports detailing absorption, distribution, metabolism and excretion of bimatoprost and its metabolite, AGN 191522, after administration of bimatoprost have been submitted previously in Lumigan. In summary, bimatoprost was rapidly absorbed and well distributed in the rabbit and monkey eyes following ocular administration. Bimatoprost demonstrated good *in vitro* penetration across human cornea and sclera. Systemic exposure after ocular dosing was low in the rabbit, monkey, and man. AGN 191522 was not detected in humans after ocular dosing, due to the low systemic

exposure of the parent. Bimatoprost was only minimally metabolised in the ocular tissues of both monkeys and humans, but was extensively metabolised in rabbit ocular tissues. After systemic administration, bimatoprost was extensively metabolised to polar metabolites in all the species tested. Both urinary and faecal routes are important pathways for elimination of bimatoprost and its metabolites in rats and monkeys.

To support the registration of the 0.01% bimatoprost/200 ppm benzalkonium chloride (BAK) ophthalmic solution, six pharmacokinetic studies were conducted to assess the ocular absorption of bimatoprost using primary cultures of rabbit cornea epithelia *in vitro*, and ocular absorption in NZW and DB rabbits *in vivo*. In addition, systemic drug exposure was assessed in one single dose study and two repeated dose toxicokinetics studies from toxicology studies.

Due to the cytotoxic properties of BAK, it is, from a safety point of view, preferable to minimise its presence in ophthalmic preparations. As part of the January 09 LoOI, the MAH was requested by the CHMP to substantiate why similar efficacy could not be obtained with a formulation containing lower BAK concentration. In order to demonstrate that maximal ocular bimatoprost absorption is obtained with a BAK concentration of 200 ppm, the MAH submitted preliminary results from a newly conducted ocular absorption study (PK-09-063). In this study, female rabbits received a single 28 µL eyedrop of 0.01% bimatoprost containing varying concentrations (50, 100, 150, 200, 300 ppm) of BAK into both eyes and aqueous humor samples were collected (n = 2-4 animals with 4-8 eyes per time point) at 0.25, 0.5, 1, 2, 3, 4 and 6 hours post-dose. The results confirm that maximal bimatoprost ocular absorption is obtained with 200 ppm BAK.

From the preliminary analysis of the newly conducted study, it appears that aqueous humour C_{max} for the major bimatoprost metabolite AGN-191522 occurs 2 hours following ocular administration of 0.01% bimatoprost/200 ppm BAK. In comparison, AGN-191522 T_{max} is 1 hour following Lumigan administration to rabbits. In the originally submitted reports, the aqueous humour concentration of AGN-191522 was only evaluated 1 hour following ocular administration of Lumigan and 0.01% bimatoprost/200 ppm BAK, hence this finding may explain why lower AGN-191522 concentrations were obtained with 0.01% bimatoprost/200 ppm BAK relative to Lumigan (study PK-06-108).

The CHMP considered that the MAH has substantiated that maximal bimatoprost ocular absorption is obtained in rabbits with 200 ppm BAK relative to 50, 100, 150, and 300 ppm. The issue was considered resolved. However, the MAH is requested to submit the full report for study PK-09-063 for review upon its completion.

Toxicology

The toxicity profile of bimatoprost has been well characterised during studies conducted to support registration of Lumigan. Evaluations include single-dose toxicity, repeated-dose toxicity, reproductive toxicity, genotoxicity, carcinogenicity, and antigenicity. Extensive ocular and systemic toxicological studies have been conducted in a number of animal species to establish the preclinical safety of Lumigan.

Additional repeat-dose ocular toxicity studies of 1-month and 6-month duration were conducted in NZW and DB rabbits, respectively, to support registration of 0.01% bimatoprost/200 ppm BAK ophthalmic solution. The doses administered were similar to that administered clinically in humans.

In the 1-month ocular toxicity study, conjunctival congestion, mostly mild, was transiently observed with all formulations containing 200 ppm BAK including the placebo, whereas conjunctival congestion was not observed in untreated eyes or rabbits given Lumigan (50 ppm BAK). In addition, all the formulations contained 200 ppm BAK resulted in minimal to mild corneal epithelial degeneration and regeneration and/or corneal stromal oedema in most treated eyes. Moreover, a minimal goblet cell loss was observed in the conjunctival mucosa. It appears that BAK-induced corneal epithelial alterations is dose-dependent.

On the other hand, no treatment-related findings were made in a 6-month ocular repeat-dose toxicity study comparing two different concentrations of bimatoprost (0.01% and 0.0125%) both formulated

with 200 ppm BAK. The MAH justified the lack of using Lumigan (50 ppm BAK) as comparator due to the absence of findings for Lumigan in a previous 6-month ocular safety study.

A large number of scientific articles report on the ocular toxicity of BAK in various non-clinical models. Hence, based on non-clinical data, it cannot be excluded that the new 0.01% bimatoprost/200 ppm BAK formulation may adversely affect the human eye. However it should be borne in mind that the rabbit appears to be more sensitive towards ocular toxicants than humans, e.g., rabbits have a greatly reduced blinking rate compared to humans and BAK appears to induce a higher degree of tight junction disruption in rabbits than in humans. On the other hand, epidemiological as well as small clinical studies have indicated that long-term treatment with BAK preserved eye drops induces ocular changes.

The antigenicity of bimatoprost has been evaluated previously to support registration of Lumigan.

Bimatoprost does not appear to have a phototoxic potential.

Based on the data submitted by the MAH, the use of Lumigan 0.01% is unlikely to represent a risk for the environment when used in the proposed indication and recommended dose.

4. Clinical aspects

Pharmacokinetics
Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration, the systemic exposure of bimatoprost is very low, with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025ng/ml) within 1.5 hours after dosing. Mean C_{max} and AUC $_{0\text{-}24hrs}$ values were similar on days 7 and 14 at approximately 0.08ng/ml and 0.09 ng·hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 l/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a variety of metabolites.

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 l/hr/kg.

No new clinical studies have been conducted to further explore the pharmacokinetics of bimatoprost. Data submitted have been the clinical pharmacokinetics of bimatoprost 0.03% which had been previously assessed for the Lumigan application. This is considered acceptable as Lumigan has been marketed for 7 years and the pharmacokinetic profile of the active substance is well known. Moreover, the content of bimatoprost has been decreased to one third and thus, it is expected that the systemic drug exposure will not be increased with the proposed new strength.

Pharmacodynamics
No new phamacodynamic studies have been submitted.

Bimatoprost is a synthetic analogue of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Its pharmacology is conferred by replacement of the carboxylic acid group of $PGF_{2\alpha}$ with an ionically neutral substituent. Since the carboxylic acid group is critical for interaction with $PGF_{2\alpha}$ -sensitive FP receptors, bimatoprost

exhibits no meaningful pharmacological activity at FP receptors. Extensive studies have shown that bimatoprost has no meaningful pharmacological activity at all other known prostaglandin receptors.

Bimatoprost appears to mimic the activity of a newly discovered, naturally occurring substance that has been termed prostamide $F_{2\alpha}$ ($PGF_{2\alpha}$ 1-ethanolamide). Prostamide $F_{2\alpha}$ is biosynthetically derived from anandamide by a pathway that involves COX-2, but not COX-1. This novel pathway, named the prostamide pathway, leads to the biosynthesis of novel lipid amides that lower intraocular pressure. The prostamide pathway may be viewed as running parallel to the arachidonic acid cascade. Both pathways lead to the formation of naturally occurring ocular hypotensive products, prostamides and prostaglandins, respectively.

The lack of new pharmacodynamic studies are justified by the fact that the pharmacology of bimatoprost is well characterised.

Clinical efficacy

The following studies were conducted. It should be noted that studies 192024-030 (pilot study), 192024-031 (pivotal) and 192024-035 (supportive) investigate the sought bimatoprost 0.01 % formulation with 200 ppm BAK.

Table 2.7.3.1-1 Summary of Phase 2 and 3 Clinical Efficacy and Safety Studies

Study/Report No.	Phase	Population (ITT)	Key Features
192024-020[a]	2	OHT or glaucoma (N = 188)	Bimatoprost 0.01% BID, 0.015% BID, 0.02% QD, 0.025% QD compared to LUMIGAN® (all with **50 ppm BAK**) and Timolol 0.5% Double-masked, 6-arm parallel-group Twice daily: study medication morning and evening Once daily: vehicle morning, study medication evening 1-month primary analysis
192024-030	2	OHT or glaucoma (N = 249)	Bimatoprost 0.01% QD, 0.015% QD, 0.015% QD/EDTA, 0.02% QD (all with **200 ppm BAK**) compared to LUMIGAN® (with **50 ppm BAK**) Double-masked, paired-eye Once daily, morning dosing, one eye test formulation, the other eye LUMIGAN® 5-day
192024-031	3	OHT or glaucoma (N = 561)	Bimatoprost 0.01% QD, 0.0125% QD (with **200 ppm BAK**) compared to LUMIGAN® (with **50 ppm BAK**) Double-masked, 3-arm, parallel-group Oncedaily, evening dosing 3-month primary analysis period followed by 9-month masked extension
192024-035	2	OHT or glaucoma controlled with latanoprost 0.005% (N = 222)	Bimatoprost 0.01% (**200 ppm BAK**) and vehicle (**200 ppm BAK**) Double-masked, 2-arm, vehicle-controlled Once daily, evening dosing 1-month

Source: Reports 192024-020, 192024-030, 192024-031, and 192024-035 Module 5.3.5.1

BAK = benzalkonium chloride; BID = twice daily; EDTA = ethylamine diamine tetraacetic acid; ITT = intent-to-treat; OHT = ocular hypertension; QD = once daily.

a Phase 2 Study, 192024-020, was not part of the clinical development programme for Bim 0.01% but provides supportive efficacy and safety data for the choice of bimatoprost concentrations in Studies 192024-030, 192024-031, and 192024-035.

With the Response to the CHMP D 120 LoQ the MAH submitted study 192024-035, a double masked comparison of bimatoprost 0.01 % versus vehicle (see below).

Dose-response studies and main clinical studies

192024-020

This was a randomised, double-masked, 6-armed multi-centre comparison of several concentrations and dosing regimen of bimatoprost to Lumigan and timolol eye drops in patients with glaucoma or ocular hypertension. The bimatoprost solutions had the same BAK concentration, namely 50 ppm as Lumigan. The following doses and regimen were tested: bimatoprost 0.01 % BID, 0.015 % BID, 0.02 % QD, and 0.025 % QD compared with Lumigan (bimatoprost 0.03 %) QD and timolol 0.5 % BID, for one month. The primary endpoint was the change in IOP from baseline.

188 patients were included. There was a statistically significant difference between the 0.03 % QD group and the other groups (pair wise comparisons) at week 1, but this did not remain at month 1. However, the numeric decrease was persistently larger with bimatoprost 0.03 % than with any other strength. The target IOP analysis (the percentage of patients who achieved a mean IOP ≤ 13 to ≤ 2 0 mm Hg) did not reveal any specific pattern.

192024-030

This phase 2 trial was a 5-day, randomised, double-masked, paired-eye multi-centre study of the safety and efficacy of the bimatoprost 0.01 %, bimatoprost 0.015 %, bimatoprost 0.015 % with EDTA, and bimatoprost 0.02 % formulations with Lumigan.

The primary efficacy variable was IOP change from baseline with Day H0 as the primary time point. Other endpoints were: IOP-readings, which were performed at H0, 4, 6 and 8 at baseline, at H 4 on Day 1 and 2, at H 4, 6, and 8 on days 3 and 4, and at H0 on Day 5. A total of 249 patients were randomised.

Results of the primary endpoint are shown below:

Table 11.4-1 Mean Change from Baseline Intraocular Pressure (mm Hg) for Each Regimen at Each Visit

Timepoint	Mean Change from Baseline Intraocular Pressure (mm Hg)			
	Bim 0.01%/ LUMIGAN N = 61	Bim 0.015% EDTA/ LUMIGAN N = 64	Bim 0.015%/ LUMIGAN N = 60	Bim 0.02%/ LUMIGAN N = 64
Day 1, Hour 4	-2.5 / -3.2	-2.5 / -2.5	-2.4 / -2.7	-2.9 / -3.0
Difference[a]	0.7[b]	0.0	0.4	0.1
(95% CI[c])	(0.12 to 1.28)	(-0.55 to 0.57)	(-0.17 to 0.91)	(-0.50 to 0.67)
Day 2, Hour 4	-3.9 / -4.6	-4.5 / -4.5	-3.9 / -4.7	-5.0 / -5.0
Difference[a]	0.7[b]	0.0	0.8[b]	-0.0
(95% CI[c])	(0.17 to 1.22)	(-0.50 to 0.50)	(0.23 to 1.37)	(-0.56 to 0.55)
Day 3, Hour 4	-4.6 / -5.0	-4.8 / -5.0	-4.9 / -5.7	-5.4 / -5.4
Difference[a]	0.4	0.2	0.8[b]	-0.0
(95% CI[c])	(-0.17 to 0.99)	(-0.33 to 0.68)	(0.18 to 1.41)	(-0.51 to 0.48)
Day 3, Hour 6	-4.9 / -5.0	-4.4 / -4.7	-4.9 / -5.4	-5.8 / -5.5
Difference[a]	0.1	0.3	0.5[b]	-0.3
(95% CI[c])	(-0.36 to 0.51)	(-0.23 to 0.78)	(0.07 to 0.93)	(-0.76 to 0.19)
Day 3, Hour 8	-4.8 / -5.6	-5.1 / -5.4	-5.1 / -5.5	-5.3 / -5.4
Difference[a]	0.8[b]	0.2	0.5	0.1
(95% CI[c])	(0.27 to 1.27)	(-0.35 to 0.78)	(-0.09 to 1.02)	(-0.33 to 0.52)
Day 4, Hour 4	-4.9 / -5.5	-5.1 / -5.0	-5.3 / -5.5	-6.0 / -5.8
Difference[a]	0.6[b]	-0.1	0.2	-0.2
(95% CI[c])	(0.10 to 1.13)	(-0.68 to 0.48)	(-0.38 to 0.86)	(-0.73 to 0.26)
Day 4, Hour 6	-5.0 / -5.4	-4.7 / -5.0	-5.1 / -5.1	-5.7 / -5.6
Difference[a]	0.4	0.2	-0.1	-0.1
(95% CI[c])	(-0.05 to 0.81)	(-0.34 to 0.81)	(-0.57 to 0.47)	(-0.62 to 0.46)
Day 4, Hour 8	-5.2 / -5.8	-4.9 / -5.0	-5.0 / -5.5	-6.1 / -5.7
Difference[a]	0.6[b]	0.1	0.4	-0.3
(95% CI[c])	(0.19 to 1.06)	(-0.45 to 0.69)	(-0.15 to 1.03)	(-0.80 to 0.14)
Day 5, Hour 0	-5.9 / -6.4	-6.1 / -6.4	-6.8 / -6.7	-6.5 / -6.6
Difference[a]	0.5[b]	0.3	-0.1	0.1
(95% CI[c])	(0.02 to 1.01)	(-0.24 to 0.80)	(-0.53 to 0.43)	(-0.49 to 0.71)

Source: Tables 14.2-1.1 to 14.2-1.4

Note: The N's at each time point may not be the same as the baseline N's, due to missing data.

a calculated as test formulation minus LUMIGAN®; values for LUMIGAN® were presented per regimen and were not pooled; a negative value favored the test formulation

b statistically significant (p 0.05) based on paired t-test for treatment difference

c 95% confidence interval for between-treatment difference

Overall, a pattern of numeric lower mean IOP decrease from baseline and higher mean IOP values with the sought bimatoprost 0.01 % concentration versus the approved Lumigan, bimatoprost 0.03 %, is evident. In 6/9 and 2/9 time points, respectively, the differences were statistically significant.

192024-031

This key study was a randomised, multi-centre, double-masked, parallel, active controlled, 3 months study with a masked 9 months extension of the safety and efficacy of bimatoprost 0.01 % and bimatoprost 0.0125 %, both preserved with BAK 200 ppm compared with bimatoprost 0.03 % preserved with BAK 50 ppm (Lumigan), dosed once daily in patients with open angle-glaucoma or ocular hypertension. The primary end point was the change in the mean IOP from baseline. Secondary endpoints were: the mean IOP, the responder rate, i.e. the percentage of patients achieving a target pressure of < 18 mm Hg at all time points, mean change from baseline IOP stratified by IOP/CCT and adjusted for CCT, mean IOP stratified by IOP/CCT and adjusted for CCT, mean diurnal IOP, mean change from baseline diurnal IOP, physician's global assessment the investigator's willingness to use the medication. Several analyses on scheduled time points for changes in conjunctival bulbar hyperaemia, graded on a 5-point scale were also performed. A total of 561 patients were randomised. Results for the primary endpoint are depicted below.

Table 11.4-2 **Mean Change from Baseline Intraocular Pressure (mm Hg) (ITT with LOCF) Non-inferiority/superiority Analysis at 1.50 mm Hg Margin**

Visit	Timepoint	Mean Change from Baseline Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 186/187	Bim 0.0125% / LUMIGAN® N = 188/187
Week 2	Hour 0	-7.3 / -7.7	-7.3 / -7.7
	Difference[a]	0.42	0.35
	(95% CI[b])	(-0.22 to 1.07)	(-0.29 to 1.00)
	Hour 4	-5.9 / -7.0	-5.9 / -7.0
	Difference[a]	1.07	1.04
	(95% CI[b])	(0.44 to 1.70)	(0.42 to 1.67)
	Hour 8	-5.4 / -6.1	-5.5 / -6.1
	Difference[a]	0.68	0.58
	(95% CI[b])	(0.05 to 1.32)	(-0.06 to 1.21)
Week 6	Hour 0	-7.5 / -7.7	-7.3 / -7.7
	Difference[a]	0.24	0.45
	(95% CI[b])	(-0.40 to 0.87)	(-0.18 to 1.09)
	Hour 4	-6.2 / -6.8	-6.2 / -6.8
	Difference[a]	0.52	0.55
	(95% CI[b])	(-0.15 to 1.20)	(-0.13 to 1.23)
	Hour 8	-5.6 / -5.8	-5.6 / -5.8
	Difference[a]	0.19	0.22
	(95% CI[b])	(-0.48 to 0.85)	(-0.44 to 0.89)
Month 3	Hour 0	-7.8 / -8.0	-7.5 / -8.0
	Difference[a]	0.19	0.46
	(95% CI[b])	(-0.45 to 0.83)	(-0.18 to 1.10)
	Hour 4	-6.3 / -7.1	-6.4 / -7.1
	Difference[a]	0.78	0.71
	(95% CI[b])	(0.09 to 1.48)	(0.01 to 1.40)
	Hour 8	-5.9 / -6.1	-5.8 / -6.1
	Difference[a]	0.24	0.33
	(95% CI[b])	(-0.44 to 0.92)	(-0.35 to 1.01)
Month 6	Hour 0	-7.4 / -7.6	-7.0 / -7.6
	Difference[a]	0.25	0.64
	(95% CI[b])	(-0.40 to 0.91)	(-0.01 to 1.30)
	Hour 4	-6.0 / -6.9	-5.8 / -6.9
	Difference[a]	0.86	1.08
	(95% CI[b])	(0.19 to 1.53)	(0.41 to 1.75)
	Hour 8	-5.7 / -6.0	-5.4 / -6.0
	Difference[a]	0.31	0.56
	(95% CI[b])	(-0.37 to 0.99)	(-0.12 to 1.23)
Month 9	Hour 0	-7.2 / -7.2	-6.8 / -7.2
	Difference[a]	-0.01	0.43
	(95% CI[b])	(-0.67 to 0.65)	(-0.23 to 1.08)
	Hour 4	-5.9 / -6.3	-5.8 / -6.3
	Difference[a]	0.45	0.56
	(95% CI[b])	(-0.22 to 1.12)	(-0.11 to 1.23)

Visit	Timepoint	Mean Change from Baseline Intraocular Pressure (mm Hg)	
		Bim 0.01% / LUMIGAN® N = 186/187	Bim 0.0125% / LUMIGAN® N = 188/187
Month 12	Hour 0	-7.4 / -7.6	-7.0 / -7.6
	Difference[a]	0.27	0.61
	(95% CI[b])	(-0.41 to 0.95)	(-0.07 to 1.29)
	Hour 4	-5.8 / -6.3	-5.6 / -6.3
	Difference[a]	0.52	0.69
	(95% CI[b])	(-0.19 to 1.24)	(-0.02 to 1.41)
	Hour 8	-5.2 / -5.6	-5.2 / -5.6
	Difference[a]	0.40	0.42
	(95% CI[b])	(-0.29 to 1.09)	(-0.27 to 1.10)

Source: Tables 14.2-1.2 to 14.2-1.7

a calculated as test formulation minus LUMIGAN®; a negative value favoured the test formulation

b 95% confidence interval for between-treatment difference based on the one-way ANOVA model with fixed effect of treatment

Statistically and clinically significant mean decreases from baseline IOP were seen with all treatments at each time point.

The primary efficacy endpoint, non-inferiority at all post-baseline time points, has not formally been fulfilled, as the difference within 1.50 mm Hg margin was obtained at 15/17 points and not in 17/17 time points. Numerically, the mean decrease in IOP and the IOP were constantly lower with bimatoprost 0.01 % than with bimatoprost 0.03 %.

The responder rate is surprisingly low for all treatment groups. The numeric differences between the Lumigan and the 2 other treatment groups in absolute figures is clear and maybe clinically relevant, although not statistically significant.

Adjusted analyses confirmed the results.

192024-035

This trial was intended to evaluate the safety and efficacy of bimatoprost 0.01 % eye drops once daily compared with vehicle administered once daily for one month in glaucoma or ocular hypertension patients whose IOP was controlled with latanoprost 0.005 % eye drops (these eye drops are preserved with 200 ppm BAK). The dosing regimen was one application daily.

The primary variable was macroscopic hyperaemia. The bulbar hyperaemia was graded compared to standard photographs on a 5-point scale: 0, + 0.5 (trace), + 1 (mild), +2 (moderate), + 3 (severe). The primary efficacy endpoint was IOP, which was measured at baseline and at Month 1 at H0 (in the morning between 7 and 9 a.m.), 4 and 8 hours after the morning determination. A number of 222 patients were recruited, of whom 151 received bimatoprost and 71 received vehicle.

For the primary endpoint an increase in the macroscopic hyperaemia from baseline, i.e. on latanoprost therapy, was observed with bimatoprost (0,18; $p<0.001$), as well as with vehicle (0.02; $p<0.581$). The former increase was considerably more pronounced than the latter. The absolute values are, though, not grave. The difference between bimatoprost and vehicle was statistically significant with 0.15 grade ($p<0.009$; 95 % CI 0.04, 0.26).The difference was, however, within the non-inferiority margin of 0.5 grades, consequently, the non-inferiority criterion was met.

For the primary efficacy endpoint, i.e. IOP, a statistically significant decrease from baseline to the 1 month observations was noted at all 3 time measure points (range -0.7 to 1.3 mm Hg; p equal to or <0.002). This observation illustrates the rather high degree of efficiency of bimatoprost in relation to latanoprost. Correspondingly, a statistically significant increase in IOP was seen in the vehicle group

with 3.3 to 3.6 mm Hg (p equal to or < 0.001). The difference between bimatoprost and vehicle ranges from – 4.06 to -4.81 mm Hg (p equal to or < 0.002).

Study 192024-002, previously submitted for Lumigan, evaluated non-preserved bimatoprost ophthalmic solutions at the 0.003%, 0.01% and 0.03% concentrations and demonstrated that the ocular hypotensive effect of bimatoprost was dose-related.

Conclusions on clinical efficacy

Efficacy has been shown for the 0.01 % bimatoprost formulation applied for in patients with glaucoma or ocular hypertension.

In the key study (192014-031), the non-inferiority margin was adequately predefined as 1.5 mm Hg, which is a generally accepted value. However, persistently numeric less favourable outcome in IOP decrease from baseline, absolute IOP values, diurnal IOP control and the number of responders was seen, although the differences between bimatoprost 0.01 % and Lumigan are not large. The numeric differences between the Lumigan and the 2 other treatment groups in absolute figures is clear and may be clinically relevant, although not statistically significant.

The primary efficacy endpoint, non-inferiority at all post-baseline time points, has not formally been fulfilled, as the difference within 1.50 mm Hg margin was obtained at 15/17 points and not in 17/17 time points. Numerically, the mean decrease in IOP and the IOP were constantly lower with bimatoprost 0.01 % than with bimatoprost 0.03 %.

Adjusted analyses confirmed the results. This also applies to all PP-analyses, pointing at robustness of the observations. The clinically important responder rate entity is numerically lower for bimatoprost 0.01 % and 0.0125 % than for Lumigan (0.03 %).

Although efficacy was shown for bimatoprost 0.01 % ,the results were consistently numerically inferior (approximately 0.5 mm/Hg) when compared with Lumigan 0.03 %. The cliical relevance of this difference is unknown.

In the study 192024-035, an increase in the macroscopic hyperaemia from baseline, i.e. on latanoprost therapy, was observed with bimatoprost (0, 18; p<0.001), as well as with vehicle (0.02; p<0.581). The difference between bimatoprost and vehicle was statistically significant with 0.15 grade (p<0.009; 95 % CI 0.04, 0.26).The difference was, however, within the non-inferiority margin of 0.5 grades, consequently, the non-inferiority criterion was met.

For the primary efficacy endpoint, i.e. IOP, a statistically significant decrease from baseline to the 1 month observations was noted at all 3 time measure points (range -0.7 to 1.3 mm Hg; p equal to or < 0.002). Correspondingly, a statistically significant increase in IOP was seen in the vehicle group with 3.3 to 3.6 mm Hg (p equal to or < 0.001). The difference between bimatoprost and vehicle ranges from – 4.06 to -4.81 mm Hg (p equal to or < 0.002). This study supports the high degree of clinical efficacy of bimatoprost 0.01% in terms of IOP-decreasing properties.

Clinical safety

Patient exposure

The number of exposed subjects is depicted below:

Table 2.7.4.1.2-1 Studies 192024-030, 192024-031, and 192024-035: Number of Subjects Exposed to Bimatoprost Formulations

		Number of Subjects		Number of Subjects Evaluable for Safety[b] in Each Treatment Arm						
Study Number	Duration of Therapy	ITT[a]	Evaluable for Safety[b]	Bim 0.01% QD (9668X[g])	Bim 0.0125% QD (9721X[g])	Bim 0.015% QD (9669X[g])	Bim[c] 0.015% QD (9673X[g])	Bim 0.02% QD (9670X[g])	LUMIGAN® QD (9106X[g])	Vehicle QD (9755X)
192024-030[d]	5 days	249	249	61	NA	60	64	64	249[d]	NA
192024-031[e]	12 months	561	560[f]	185	188	NA	NA	NA	187	NA
192024-035[g]	1 month	222	221	150	NA	NA	NA	NA	NA	71
Overall total		**1032**	**1030**	**396**	**188**	**60**	**64**	**64**	**436[d]**	**71**

Source: Reports 192024-030, Table 14.1-1, Module 5.3.5.1; 192024-031, Table 14.1-1, Module 5.3.5.1; and 192024-035, Table 14.1-1, Module 5.3.5.1

Bim = bimatoprost; ITT = intent-to-treat; NA = not applicable; QD = once daily.

a Allocated to receive study treatment

b Enrolled patients who received at least one dose of study medication (safety population)

c This formulation of Bimatoprost 0.015% contained EDTA as well as BAK

d In Study 192024-030, patients received one of the bimatoprost formulations in one eye and LUMIGAN® in the other eye

e Study design: 3-month, with 9-month masked extension

f One patient in the ITT population was excluded from the safety analysis because the patient was inadvertently randomised (Bim 0.01% group) despite failing the screening criteria and was subsequently discontinued from the study without receiving any study medication.

g Formulation number.

The total exposure is shown in the table below:

Table 2.7.4.1.2-3 Exposure to Bimatoprost in the Bim 0.01% and LUMIGAN® arms during the Clinical Studies

	Study 192024-031		Study 192024-030		Study 192024-035
	Bim 0.01%[a]	**LUMIGAN®**	**Bim 0.01%[a]**	**LUMIGAN®**	**Bim 0.01%[a]**
Duration of treatment	12 months	12 months	5 days	5 days	1 month
Dosing regimen	1 drop QD	1 drop QD	1 drop QD	1 drop QD	1 drop QD
Drop size	~28 µL	~28 µL	~28 µL	~28 µL	~28 µL
Approximate daily dose per eye	2.8 µg	8.4 µg	2.8 µg	8.4 µg	2.8 µg
Total dose for duration of study	2.044 mg (both eyes)	6.132 mg (both eyes)	0.014 mg (one eye)	0.042 mg (one eye)	0.157 mg (both eyes)
Daily dose for 60-kg person	0.093 µg/kg (both eyes)	0.280 µg/kg (both eyes)	0.047 µg/kg (one eye)	0.140 µg/kg (one eye)	0.093 µg/kg (both eyes)

Source: Reports 192024-031, 192024-030, and 192024-035 Module 5.3.5.1

Bim = bimatoprost; QD = once daily.

The demographic features of the exposed population are shown below:

Table 2.7.4.1.3-1 Studies 192024-030, 192024-031, and 192924-035: Demographics (Safety Population)

	Category	Study 192024-031 N = 560	Study 192024-030 N = 249	Study 192024-035 N = 218 [a]	All Patients in Studies N = 1027
Age	Mean (range)	63.5 (23-94)	64.4 (21-88)	64.9 (24-90)	63.8[b] (21-94)
years	< 45	26 (4.6%)	13 (5.2%)	11 (5.0%)	50 (4.9%)
	45-65	279 (49.8%)	109 (43.8%)	97 (44.5%)	485 (47.2%)
	> 65	255 (45.5%)	127 (51.0%)	110 (50.5%)	492 (47.9%)
Gender	Male	239 (42.7%)	108 (43.4%)	87 (39.9%)	434 (42.3%)
n (%)	Female	321 (57.3%)	141 (56.6%)	131 (60.1%)	593 (57.7%)
Race	Caucasian	408 (72.9%)	204 (81.9%)	157 (72.0%)	769 (74.9%)
n (%)	Black	76 (13.6%)	28 (11.2%)	56 (25.7%)	160 (15.6%)
	Hispanic	65 (11.6%)	13 (5.2%)	0 (0.0%)	78 (7.6%)
	Asian	7 (1.3%)	4 (1.6%)	5 (2.3%)	16 (1.6%)
	Other	4 (0.7%)	0 (0.0%)	0 (0.0%)	4 (0.4%)
Ophthalmic[d]	OHT	262 (46.8%)	102 (41.0%)	43 (19.7%)	407 (39.6%)
Diagnosis	Glaucoma[c]	289 (51.6%)[c]	147 (59.0%)	169 (77.5%)	605 (58.9%)
	Glaucoma/OHT	9 (1.6%)	0 (0.0%)	6 (2.8%)	15 (1.5%)
Types of	Chronic OAG[c]	289 (51.6%)[c]	NA	NA	NA
Glaucoma[d]	Chronic OAG with patent iridotomy/ iridectomy	3 (0.5%)	NA	NA	NA
	Pseudoexfoliative glaucoma	5 (0.9%)	NA	NA	NA
	Pigmentary glaucoma	3 (0.5%)	NA	NA	NA

Source: Reports 192024-031, Tables 14.1-2.3 and 14.1-3, Module 5.3.5.1; 192024-030, Tables 14.1-2 and 14.1-4, Module 5.3.5.1; and 192024-035, Tables 14.1-2 and 14.1-3, Module 5.3.5.1

NA = not available; OAG = open angle glaucoma; OHT = ocular hypertension.

a Modified ITT population (Bim 0.01% = 147, vehicle = 71), which included all randomized patients who received at least 1 dose of study medication and who were evaluated for macroscopic hyperaemia at all 3 timepoints at baseline and the Month 1 visits. Four patients in the safety population (all Bim 0.01%) were excluded from the mITT population.

b Calculated as weighted mean

c Study 192024-031: Patient 3276-33442 with chronic OAG was excluded from the safety analysis

d ITT population

An overall summary of reported adverse events in the 3 trials is shown in the table below:

Table 2.7.4.2.1-1 Overall Summary of Adverse Events

	Study 192024-031			Study 192024-030		Study 192024-035	
	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187	Bim 0.01% N = 61	LUMIGAN® N = 249	Bim 0.01% N = 150	Vehicle N = 71
All adverse events	121 (65.4%)[b]	125 (66.5%)[c]	145 (77.5%)	NA		30 (20.0%)	9 (12.7%)
- ocular	88 (47.6%)[b]	92 (48.9%)[c]	116 (62.0%)	19 (31.1%)	93 (37.3%)	24 (16.0%)[e]	6 (8.5%)[e]
- non-ocular	80 (43.2%)	69 (36.7%)	77 (41.2%)	2 (3.3%)		NR	NR
Treatment-related AEs	71 (38.4%)[b]	75 (39.9%)[c]	95 (50.8%)	NA		23 (15.3%)	5 (7.0%)
- ocular	70 (37.8%)[b]	75 (39.9%)[c]	94 (50.3%)	16 (26.2%)	86 (34.5%)	21 (14.0%)[e]	4 (5.6%)[e]
- non-ocular	2 (1.1%)	0 (0.0%)	3 (1.6%)	0 (0.0%)		NR	NR
SAEs	17 (9.2%)	11 (5.9%)	14 (7.5%)	0 (0.0%)		0 (0.0%)	0 (0.0%)
Treatment-related SAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)
Deaths	1 (0.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)
Discontinuation due to AEs	8 (4.3%)	8 (4.3%)	14 (7.5%)	0 (0.0%)		2 (1.3%)	0 (0.0%)
- ocular AEs[d]	4 (2.2%)[b]	6 (3.2%)	12 (6.4%)	0 (0.0%)		2 (1.3%)	0 (0.0%)
Discontinuation due to treatment-related AEs	4 (2.2%)	5 (2.7%)	12 (6.4%)	0 (0.0%)		2 (1.3%)	0 (0.0%)

Source: Report 192024-031, Tables 14.3-3.1, 14.3-4.1, 14.3-5, 14.3-6, 14.4 -5.2, 14.6-1.1, 14.6-2.1 and 14.6-8 and Listings 16.2.1-2 and 16.2.7-2, Module 5.3.5.1; Report 192024-030, Tables 14.3-4 to 14.3-10, Module 5.3.5.1; and Report 192024-035, Tables 14.3-6, 14.3-9, and 14.3-11, Module 5.3.5.1

AE = adverse event; Bim = bimatoprost; NA = not applicable; NR = not reported; SAE = serious adverse event.

a Study 192024-030: Patients received test treatment in one eye and LUMIGAN® in the other eye. The Bim 0.015% EDTA, Bim 0.015% and Bim 0.02% treatment groups are not presented in table

b Bim 0.01% significantly less than LUMIGAN® (p = 0.043)

c Bim 0.0125% significantly less than LUMIGAN® (p = 0.044)

d Log-rank test performed to analyse the time to discontinuation of patients

e For Study 192024-035, ocular adverse events were not summarized separately; numbers here are the number of eye disorder SOC adverse events.

Adverse events

As the 2 clinical studies 192024-030 and 192024-031 were of a different design (the former being a pair-wise comparison between the 2 eyes, and the latter being a parallel group study), and the doses applied were different from the formulation of bimatoprost applied for the data are not pooled. In the double –masked study 192024-035 with bimatoprost 0.01 % versus vehicle the patients were switched directly from latanoprost treatment to either active or vehicle.

A review of the recorded ocular adverse events is depicted below.

Table 2.7.4.2.1-3 Studies 192024-031, 192024-030, and 192024-035: Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by ≥ 1% of Patients in Any Active Treatment Group

SOC Preferred Term[a]	Study 192024-031			Study 192024-030		Study 192024-035	
	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187	Bim 0.01% N = 61	LUMIGAN® N = 249	Bim 0.01% N = 150	Vehicle N = 71
All Ocular Events	88 (47.6%)[b]	92 (48.9%)[c]	116 (62.0%)	19 (31.1%)	93 (37.3%)	24 (16.0%)[e]	6 (8.5%)[e]
Eye disorders							
Conjunctival hyperaemia	58 (31.4%)	50 (26.6%)[c]	73 (39.0%)	12 (19.7%)	66 (26.5%)	10 (6.7%)	2 (2.8%)
Erythema of eyelid	7 (3.8%)	6 (3.2%)	10 (5.3%)	0 (0.0%)	5 (2.0%)	1 (0.7%)	0 (0.0%)
Eye irritation	7 (3.8%)	5 (2.7%)	3 (1.6%)	1 (1.6%)	12 (4.8%)	0 (0.0%)	0 (0.0%)
Growth of eyelashes	7 (3.8%)	2 (1.1%)	6 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Conjunctival haemorrhage	5 (2.7%)	2 (1.1%)	1 (0.5%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Vision blurred	5 (2.7%)	0 (0.0%)[d]	3 (1.6%)	0 (0.0%)	2 (0.8%)	3 (2.0%)	1 (1.4%)
Punctate keratitis	4 (2.2%)	6 (3.2%)	11 (5.9%)	0 (0.0%)	4 (1.6%)	1 (0.7%)	0 (0.0%)
Cataract	4 (2.2%)	5 (2.7%)	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye pruritus	4 (2.2%)	2 (1.1%)[c]	10 (5.3%)	4 (6.6%)	8 (3.2%)	4 (2.7%)	1 (1.4%)
Conjunctival oedema	3 (1.6%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visual acuity reduced	2 (1.1%)	8 (4.3%)	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye pain	2 (1.1%)	1 (0.5%)	2 (1.1%)	3 (4.9%)	5 (2.0%)	1 (0.7%)	0 (0.0%)
Eyelids pruritus	2 (1.1%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	2 (0.8%)	0 (0.0%)	0 (0.0%)
Vitreous floaters	2 (1.1%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Asthenopia	1 (0.5%)	1 (0.5%)	3 (1.6%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Vitreous detachment	1 (0.5%)	1 (0.5%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Foreign body sensation in eyes	0 (0.0%)	5 (2.7%)	5 (2.7%)	0 (0.0%)	0 (0.0%)	1 90.7%)	1 (1.4%)

Table 2.7.4.2.1-3 Studies 192024-031, 192024-030, and 192024-035: Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by ≥ 1% of Patients in Any Active Treatment Group (continued)

SOC Preferred Term[a]	Study 192024-031			Study 192024-030		Study 192024-035	
	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187	Bim 0.01% N = 61	LUMIGAN® N = 249	Bim 0.01% N = 150	Vehicle N = 71
Dry eye	0 (0.0%)	5 (2.7%)	3 (1.6%)	0 (0.0%)	6 (2.4%)	3 (2.0%)	2 (2.8%)
Blepharitis	0 (0.0%)	3 (1.6%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Abnormal sensation in eye	0 (0.0%)	2 (1.1%)	3 (1.6%)	3 (4.9%)	12 (4.8%)	2 (1.3%)	1 (1.4%)
Eye allergy	0 (0.0%)	2 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Iris hyperpigmentation	0 (0.0%)	2 (1.1%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Maculopathy	0 (0.0%)	1 (0.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Scotoma	0 (0.0%)	1 (0.5%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Blepharitis allergic	0 (0.0%)	0 (0.0%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Corneal erosion	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Photophobia	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)
Lacrimation increased	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (1.6%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Conjunctival follicles	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	3 (1.2%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions							
Instillation site irritation	2 (1.1%)	3 (1.6%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections and infestations							
Hordeolum	1 (0.5%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations							
Intraocular pressure increased	0 (0.0%)	1 (0.5%)	3 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2.7.4.2.1-3 Studies 192024-031, 192024-030, and 192024-035: Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by ≥ 1% of Patients in Any Active Treatment Group (continued)

SOC Preferred Term[a]	Study 192024-031			Study 192024-030		Study 192024-035	
	Bim 0.01% N = 185	Bim 0.0125% N = 188	LUMIGAN® N = 187	Bim 0.01% N = 61	LUMIGAN® N = 249	Bim 0.01% N = 150	Vehicle N = 71
Nervous system disorders							
Visual field defect	1 (0.5%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders							
Skin hyperpigmentation	5 (2.7%)	1 (0.5%)[c]	10 (5.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertrichosis	3 (1.6%)	3 (1.6%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hair growth abnormal	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Reports 192024-031, Tables 14.3-3.1 and 14.3-3.2, Module 5.3.5.1; 192024-030, Table 14.3-4, Module 5.3.5.1; and 192024-035, Table 14.3-6, Module 5.3.5.1

Bim = bimatoprost; SOC = system organ class.

a Coding based on MedDRA versions 9.1, 10.0, and 11.0 for Studies 192024-030, -031, and -035, respectively

b Bim 0.01% significantly less than LUMIGAN® ($p = 0.005$)

c Bim 0.0125% significantly less than LUMIGAN® ($p \leq 0.018$)

d Bim 0.0125% significantly less than Bim 0.01% ($p = 0.029$)

e For Study 192024-035, ocular adverse events were not summarized separately; numbers here are the number of eye disorder SOC adverse events.

The following parameters were all statistically significantly less frequent in the bimatoprost 0.01 % group than in the Lumigan group: Ocular adverse events, discontinuations due to ocular adverse events, and all adverse events, which were driven by the ocular adverse events ($p \leq 0.043$). The difference is seemingly more pronounced in the parallel group study of longer duration.

Ocular adverse events

The most common ocular adverse events with Bimatoprost 0.01% were conjunctival hyperaemia, erythema of eyelid, eye irritation, growth of eyelashes, eye pruritus, eye pain and abnormal sensation in the eye. The majority of ocular adverse events were of mild severity.

There were no reports of cystoid macular oedema, uveitis or iritis in the Bimatoprost 0.01% group in any clinical study. Changes in iris colour, interpreted as iris hyperpigmentation was noted in 2 patients in the bimatoprost 0.01 % group, in 2 patients in the Bimatoprost 0.0125% group and 1 patient in the Lumigan 0.03 % group.

Ocular adverse events were, overall, less frequent with the bimatoprost 0.01 % formulation compared to Lumigan. This was particularly noticed for conjunctival hyperaemia, punctate keratitis and erythema of the eyelid. The 2 cases interpreted as iris hyperpigmentation are not included in the bimatoprost 0.01 % group above. There is no clear preponderance of ocular adverse events with the 0.0125 % formulation as compared to the 0.01 % strength. The shorter duration Phase 2 studies, suggest that bimatoprost 0.01% had fewer ocular adverse events overall compared with Lumigan 0.03% (study -030) and more than vehicle (study -035).

Overall, these data suggest that Bimatoprost 0.01% might have a better tolerability profile than Lumigan. Surprisingly, some AEs related to ocular surface damage such as punctate keratitis and dry eye were reported more frequently in the Lumigan treatment arm. Ocular symptomatology as well as assessment of tear film, as a measure of ocular surface damage, have not been systematically assessed/recorded in the pivotal study. Except for conjunctivae hyperaemia, the incidence of ocular AEs is unexpectedly low. Thus, conclusions favouring one of the formulations can not be drawn.

Serious adverse events and deaths

Three deaths were reported from the clinical studies (all in the 192024-031 trial), all of which were regarded as not related to study medication. The causes were malignant lung neoplasm, cerebral haemorrhage, and myocardial infarction, which were reported from 82 to 252 days after onset of the treatment.

Laboratory findings

No laboratory evaluations were performed.

Safety related to drug-drug interactions and other interactions

No specific drug-drug or drug-food interaction studies were performed with Bimatoprost 0.01%. The clinical studies allowed concomitant use of artificial tear products, and other systemic therapies were permitted. However, no change to the dosing regimen was made throughout the studies to those medicines that could impair the interpretation of the results, e.g. beta adrenergic blocking agents.

Discontinuation due to AES

In study 192024-030, no patient discontinued because of adverse events.

In study 192024-031, 30 patients discontinued due to adverse events: 4.3% (8/185) of patients receiving Bimatoprost 0.01%, 4.3% (8/188) with Bimatoprost 0.0125%, and 7.5% (14/187) with Lumigan ($p= 0.285$). 21 patients discontinued because of treatment related adverse events. The treatment-related causes of discontinuation from the Bimatoprost 0.01% group were mild conjunctival hyperaemia in 2 patients, mild conjunctival hyperaemia and eye pruritus in 1 patient, and moderate vision blurred, instillation site irritation, headache and nausea in another patient. All of the discontinuations due to ocular adverse events in the Bimatoprost 0.01% group occurred in the first months of usage. Nine patients discontinued due to conjunctival hyperaemia across all treatment groups: 3 from the Bimatoprost 0.01% group, 1 from the Bimatoprost 0.0125% group and 5 from the

Lumigan group. The incidence of patients who discontinued due to ocular adverse events was 2.2 % (4/185) with Bimatoprost 0.01%, 3.2 % (6/188) with Bimatoprost 0.0125%, and 6.4% (12/187) with Lumigan (p = 0.088). One patient discontinued due to treatment-related non-ocular adverse events in the Bimatoprost 0.01% group. Intermittent nausea and headache occurred in the same patient on Day 1. The patient also experienced instillation site irritation and blurred vision. The events resulted in discontinuation but resolved without sequelae.

The discontinuation rate due to ocular adverse events and conjunctival hyperaemia are numerically lower with bimatoprost 0.01 % than with Lumigan. However, the differences are small. Four patients in the bimatoprost 0.01 % group versus 12 patients in the Lumigan group withdrew because of treatment-related adverse events. The relevance of these differences isunknown.

In study 192024-035, two patients discontinued because of ocular events, in both cases regarded as treatment related, and both patients received bimatoprost. The reports encompassed moderate conjunctival hyperaemia, moderate vision blurred and moderate eye pruritus, and, respectively, moderate photophobia.

Conclusions on clinical safety

In the trials, a total of 1030 patients with open-angle glaucoma or ocular hypertension were evaluated for safety, of whom 396 received bimatoprost 0.01 %, and of these patients, 185 were exposed for 12 months.

Overall, ocular adverse events were less frequent with the bimatoprost 0.01 % formulation than with Lumigan 0.03 %. This was particularly noticed for conjunctival hyperaemia, but also erythema of the eyelid, punctate keratitis, eye pruritus, foreign body sensation, corneal erosion, and skin hyperpigmentation (that is regularly mentioned as a complaint by the patients) occurred less frequently.

In view of the increased BAK dosage, the clinical relevance of the higher frequency in the bimatoprost 0.01 % group of eye irritation, conjunctival haemorrhage and conjunctival oedema is a matter of concern and should be established.

Regarding treatment-related adverse events, eye irritation is reported more often in the bimatoprost 0.01 % group. For neither ocular nor treatment related ocular adverse events a better profile of the 0.01 % formulation as compared to the 0.0125 % formulation is obvious.

Iris hyperpigmentation was found in 2 patients in both the Bimatoprost 0.01% group and the Bimatoprost 0.0125% group, and 1 patient in the Lumigan group. There were no cases of uveitis, iritis, cystoid macular oedema reported in patients receiving Bimatoprost 0.01%. There were no indications of a more pronounced progression of glaucoma with the weaker bimatoprost 0.01 % formulation than with Lumigan 0.03 % in the 12-months study.

Four patients in the bimatoprost 0.01 % group versus 12 patients in the Lumigan group withdrew because of treatment related adverse events. Considering the compliance with any medical anti-glaucoma therapy, the clinical significance of these observations is not clear. Furthermore, 3 withdrew in bimatoprost 0.01% group due to conjunctival hyperemia, whereas 5 patients withdrew for the same reasons in the Lumigan group, which was not considered a relevant finding. In the 192024-035 trial two patients treated with bimatoprost 0.01 % discontinued because of adverse events. No new ocular adverse events were reported with the increased BAK concentration.

Some CHMP members expressed concerns that the new 0.01 % formulation may be associated with increased ocular toxicity than Lumigan 0.03% in the long-term, due to the increase in BAK concentration. Corneal tissue damage was not systematically evaluated in the clinical studies in support of this application, and studies were not sufficiently long to assess this damage. The potential consequences for the target population will have to be investigated and thus a post-marketing study will need to be carried out.

Additionally, some CHMP members were concerned that the rationale to support the final BAK concentration of 200 ppm was based on non-clinical studies and on the fact that other available prostaglandin analogues (e.g. latanoprost) contain the same concentration, which is not, *per se*, entirely reassuring for them, especially given the 4-fold increment in the dose of BAK. Some CHMP members also expressed their dissatisfaction for the fact that clinical trials comparing different BAK concentrations would have been necessary to establish the most appropriate amount of BAK, and be able to avoid unnecessarily high amounts of this preservative in the new formulation.

However, given the new changes introduced in the Product Information and Allergan's commitment to investigate the potential consequences for the target population in a post-marketing study, following the Oral Explanation the majority of the CHMP considered that the safety concerns had been sufficiently addressed.

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

Risk Management Plan
As part of their responses to the LoOI adopted by the CHMP in January 2009, the MAH submitted an updated version of the risk management plan (version 03). A summary of its assessment is provided below:

The CHMP, having noted version 3 of the RMP, considered that cardiovascular events and off-label use had been satisfactorily addressed. The targeted pharmacovigilance proposed by the MAH was also acceptable to the CHMP. Regarding potential for off-label use, the MAH proposed a targeted questionnaire to distinguish among Lumigan 0.3mg/ml, Lumigan 0.1 mg/ml and Latisse (approved in the US for treatment of hypotrichosis of eyelashes), to determine whether the product was obtained with or without prescription, and to determine the indication for use. The CHMP considered this proposal to be acceptable.

Additionally, the MAH proposed a post-marketing study to compare the long-term ocular surface safety (including BAK-related corneal toxicity) between the two formulations of bimatoprost (0.1 and 0.3 mg/ml), to provide data on clinical practice patterns and incidence of ocular surface events, and to improve the knowledge of the risk factors for AEs. Only a brief summary of the study protocol was been included in the RMP.

Populations with important missing information have been addressed in the pharmacovigilance plan and the proposal of routine pharmacovigilance activities is adequate.

The MAH agreed with the CHMP that ADRs that have been required to be monitored in PSURs are already signals (iris pigmentation, corneal oedema, corneal ulcer, reactivation of corneal infiltrates, choroidal effusion, reactivation of previous infective ocular disease, increase in IOP, cardiovascular events, and asthma). These ADRs have been included in the RMP as important risks.

Finally, appropriate data on clinical trial exposure included in version 3 of the RMP was considered satisfactory by the CHMP.

However, the CHMP was of the opinion that version 3 of the RMP needed improvement.

In order for it to be approvable, the Risk Minimization Plan needed to address important potential risks others than asthma [i.e. choroidal effusion, increase in IOP, reactivation of corneal infiltrates, reactivation of previous infective ocular disease, cardiovascular events (angina, bradycardia, hypotension), and potential for off-label use]. The CHMP considered that at least provision of information in the SPC was necessary in order to reduce the risks associated with these concerns and that RMP should adequately refer to this risk minimization strategy.

Version 3 of the RMP included BAK-related corneal toxicity as an important identified risk. However, adequate measures needed to be identified and implemented to monitor and ascertain the risk to the cornea associated with use of 200 ppm BAK, supplemented by appropriate amendments to section 4.3. and 4.4 of the SPC, as necessary.

Additionally, Version 3 of the RMP also included cardiovascular adverse events (angina, bradycardia, hypotension) as important potential risks. Their epidemiology in glaucoma-patients was discussed and cardiac disorders have been included among the pharmacological class effects. However, no risk minimization activities have been proposed.

Furthermore, Version 3 of the RMP included potential for off-label use as important potential risks. However, no risk minimization activities have been proposed.

Finally, the CHMP did not agree that no additional risk minimization activities are required for choroidal effusion, increase in IOP, reactivation of corneal infiltrates and reactivation of previous ocular disease. At least, routine risk minimization activities and information in the SPC were considered necessary.

In summary, in September 2009, three were the main CHMP concerns with regards to RMP and risk minimisation:

a - Provision of information in the SPC was be necessary in order to reduce the risks associated with these concerns and that Risk Management Plan (RMP) had to adequately refer to this risk minimization strategy.

b - The section "Populations not studied in the pre-authorisation phase" of the RMP had to be amended, since pregnancy was addressed in two different paragraphs. The first one deals with pregnancy and the second one addressed both pregnancy and lactation. The first one was to be deleted, since information regarding the number of pregnancies (three) was outdated.

c - In section "Post authorisation experience" of the RMP, the CHMP recommended, in order to increase the accuracy of the wording of the section, that the sentence referring to events required to be monitored (i.e. iris pigmentation, corneal oedema, corneal ulcer, reactivation of corneal infiltrates, choroidal effusion, reactivation of previous infective ocular disease, increase in intraocular pressure, cardiovascular events, and asthma) and stated that no safety signals have been identified for them should be deleted.

Allergan pointed out that, in order to manage the potential risks associated with BAK, the Lumigan 0.01% SPC and Package Leaflet will include relevant warnings, precautions and contraindications and the risk management plan identifies BAK-related corneal toxicity as an important identified risk. Additionally, to increase knowledge regarding the long-term effects of this formulation in a broader setting, Allergan added to the initially proposed protocol of the post-marketing study an assessment of the tear break-up time (TBUT) as part of the evaluation of the effect of the increased BAK concentration. This and other proposals were submitted by the MAH in an updated Risk Management Plan (Version 4.0).

RMP Version 4.0
To specifically address the individual concerns of the CHMP, the MAH responded pointing out that

(a) In order to monitor and manage the safety of Lumigan 0.01%, the proposed pharmacovigilance and risk management activities (see below) will allow for close assessment of the safety profile in a broader setting (i.e. real-life) and will help educate physicians and patients regarding the important risks associated with Lumigan 0.01%. In addition, a post-marketing study will help obtaining a better understanding of the long-term safety of the new Lumigan 0.01% formulation in a broader setting. The proposed modifications to the SPC relating to BAK are outlined in section V of this Assessment Report.

The CHMP considered that this concern had been satisfactorily addressed. However, the committee expressed the view that the post-marketing study should be a Randomised Controlled Trial (RCT).

(b) Allergan agreed with the CHMP comment. In the updated RMP (Version 4), the first paragraph on pregnancy in the "Populations not studied in the pre-authorisation phase" has been deleted. The CHMP considered that this concern had been satisfactorily addressed.

(c) The MAH responded that the following changes were made to the "Post authorisation experience" section of the RMP:

The proposed text will read:
In addition to the post-marketing commitments, EMEA Assessments of BIM 0.03% PSURs have requested the following adverse events be monitored and evaluated: Cardiovascular events, Asthma, Corneal oedema, Choroidal effusion, Corneal ulcer, Reactivation of previous infective ocular disease, Reactivation of corneal infiltrates, Iris pigmentation, and Increase in intraocular pressure. Since the initial request by EMEA, these events of interest have been routinely monitored through Allergan's Signal Detection Reviews and addressed in BIM 0.03% PSURs. ~~To date there have been no safety signals identified for any of these events, no changes to the BIM 0.03% product labelling have been recommended, and the EMEA Assessment Reports have not disagreed.~~ Subsequent cases involving the events of interest or events identified as potential safety signals by Allergan will be monitored and evaluated as part of ongoing Signal Detection Reviews and discussed in PSURs as appropriate.

The CHMP considered that this concern had been satisfactorily addressed.

Proposed Risk Minimisation Activities (RMP 4.0)
Iris pigmentation, punctate keratitis and BAK-related corneal toxicity have been reported following bimatoprost use in OAG and are classified as important identified risks. These events are identified and characterized either in section 4.3 (Contraindications), 4.4 (Special warnings and precautions for use) or 4.8 ("Undesirable effects") of the SPC and in the Package Leaflet and proposed SPC and PL for Lumigan 0.01%. The CHMP agreed that these sections inform both physicians and patients of these possible adverse reactions.

Choroidal effusion, increase in IOP, reactivation of corneal infiltrates, reactivation of previous ocular disease, cardiovascular events (angina, bradycardia and hypotension) and off label use (cosmetic use for eyelash growth) are included as important potential risks in the RMP. The MAH agreed that a number of the events listed as Important Potential Risks in the Risk Management Plan should be included in section 4.4 of the SPC (i.e. reactivation of corneal infiltrates, reactivation of previous infective ocular diseases, bradycardia and hypotension). Each of these issues is dealt with individually below.

Reactivation of corneal infiltrates and reactivation of previous infective ocular disease
To date the MAH has received a total of 10 cumulative reports of reactivation of significant prior ocular infection or recurrence of uveitis associated with the use of bimatoprost where causality could not be ruled out. A number of these are related to previous ocular viral infections. The MAH agrees that it is of value to the prescriber to include language within Section 4.4 Warnings and precautions for use of the SPC relating to this potential risk, as follows:
"**There have been rare spontaneous reports of reactivation of previous corneal infiltrates or ocular infections with bimatoprost 0.3 mg/ml eye drops, solution. LUMIGAN should be used with caution in patients with a prior history of significant ocular viral infections (e.g. herpes simplex) or uveitis/iritis.**" (See section V.3 of this document).

Bradycardia
A search of the data base for this event as well as reduced heart rate yielded 16 cases, three of which were considered unrelated. In the remaining cases a relationship could not be ruled out. In the majority of cases there existed a medical history of bradycardia, in some cases in association with the use of IOP lowering agents.

Hypotension
A search of the data base for this event as well as decreased blood pressure yielded 11 cases, one of which were considered unrelated and one of which was assessed as unlikely to be related. In two cases the relationship was assessed as definite or reasonably possible. In the remaining cases a relationship could not be ruled out. Where details of medical history were available, a number of patients reported previous fainting episodes or chronic low blood pressure.

Based upon these analyses of the cumulative data, the MAH considers that it is appropriate to include both bradycardia and hypotension in Section 4.4 Warnings and precautions for use of the SPC, as follows:

"LUMIGAN has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure. **There have been a limited number of spontaneous reports of bradycardia or hypotension with bimatoprost 0.3 mg/ml eye drops, solution. LUMIGAN should be used with caution in patients predisposed to low heart rate or low blood pressure.**" (see section V.3 of this document).

However, based on the CHMP assessment of PSURs 7-9 of Lumigan, the MAH proposed not to include more information on section 4.4 of the SPC regarding choroidal effusion, increase in intraocular pressure, and angina. It is considered that these concerns are adequately addressed by the proposed actions in the Pharmacovigilance Plan and that no additional risk minimisation activities beyond these are warranted.

Choroidal effusion
There have only been two reports of choroidal effusion from over a decade of exposure from either clinical trials or post-marketing experience. Only one of these was a serious case and in both cases the relationship to Lumigan usage was not clear cut but could not be ruled out. The CHMP assessment of PSURs 7-9 noted that choroidal effusion is not considered a pharmacological class effect of prostaglandins/prostamides. Accordingly, therefore, it has been agreed that this adverse event will no longer be routinely discussed in future PSURs in Section 8.4 Special Safety Analysis. However, routine Pharmacovigilance will continue. Based upon this assessment of the cumulative information the MAH did not considered appropriate to include any reference to choroidal effusion in the SPC, but its inclusion in the Risk Management Plan will continue. The CHMP considered this to be acceptable.

Increase in intraocular pressure
This event has been included as a topic in the Special Safety Analysis section of the PSUR for a number of years and has been thoroughly evaluated by both the MAH and CHMP. The Bridging Report of PSUR 7 - 9 included reference to a cumulative analysis which had been performed to support the update to the CCDS. The CHMP assessment of PSURs 7 – 9 concluded that although there are a number of reports of increased IOP, the majority of these reports were consistent with lack of efficacy or provided no information on the magnitude of the IOP increase. Furthermore, on the relatively small number of reports where an IOP spike or significantly raised IOP, was described there were either a clinically sound alternative explanation for this or insufficient details to determine a positive causality for Lumigan. The CHMP agreed that based on the review of IOP increased cases during this reporting period as well as the cumulative analysis since first product launch, there does not appear to be a safety signal for IOP increased and no labelling change is recommended. Accordingly, therefore, it has been agreed that this adverse event will no longer be routinely discussed in future PSURs in Section 8.4 Special Safety Analysis. However, routine Pharmacovigilance will continue. Therefore, the MAH proposed that reference to increased IOP would not be appropriate in the SPC, but its inclusion in the Risk Management Plan will continue. The CHMP considered this to be acceptable.

Angina
A total of 10 cases have been retrieved from the database, nine from clinical trials and the final case was a solicited report from a post marketing programme. All were considered to be unrelated to Lumigan. It is therefore considered that including this event in Section 4.4 Warnings and precautions

for use of the SPC would in fact be misleading, since there is no suggestion that there exists any link between this event and the use of bimatoprost. The inclusion of this event in the Risk Management Plan will continue. The CHMP considered this to be acceptable.

Risk Minimisation Plan (RMP Version 4.0)

In the MAH's opinion, routine pharmacovigilance and risk management activities are sufficient to monitor and evaluate the important identified and potential risks.

Conclusion on the RMP

The RMP submitted (Version 4.0) was acceptable with the provision that a post-marketing clinical trial to evaluate the comparative safety between both bimatoprost formulations be conducted in the context of the Pharmacovigilance Plan. The MAH should submit the protocol for evaluation. The CHMP recommended that Allergan consider a randomised clinical trial design for this purpose.

The need for risk minimisation activities has been discussed. Warnings related to some important potential risks have been included in section 4.4 of the SPC. The CHMP considered that the wording proposed for section 4.4 of the SPC regarding reactivation of corneal infiltrates, reactivation of previous infective ocular diseases, bradycardia and hypotension is acceptable as a risk minimisation strategy.

With regard to choroidal effusion, increase in intraocular pressure, and angina, taking into account the assessment of PSURs 7-9, the CHMP considered that these concerns are adequately addressed by the proposed actions in the Pharmacovigilance Plan and that no additional risk minimisation activities beyond these are warranted, provided that not only routine pharmacovigilance but also targeted pharmacovigilance activities are conducted to monitor these adverse effects.

Additionally, the sections "Populations not studied in the pre-authorisation phase" and "Post authorisation experience" have been properly amended.

Finally, the MAH emphasised that "*LUMIGAN 0.1 mg/ml eye drops, solution is not considered to be a replacement for LUMIGAN 0.3 mg/ml and both products will be retained in the European market."*

On the contrary, by providing physicians with therapeutic options of two formulations (one with a reduced concentration of bimatoprost or one with a low benzalkonium chloride concentration), the MAH pointed out that the goal of maximal IOP reduction combined with improved persistency in a greater number of patients overall would be achieved. It was the MAH's belief that both IOP lowering and good adherence to treatment over a long period were required to ensure the best protection of the patients against visual loss due to glaucoma.

The CHMP considered that the above sufficiently addressed the concern that Lumigan 0.03 % eye drops solution will still be available to patients.

5. Benefit Risk assessment

I.1 5.1 Clinical context

Glaucoma is a blinding disease, during the treatment of which compliance to treatment is necessary to maintain vision. Tolerability and persistence with treatment are the biggest issues with IOP-lowering medications. Lumigan 0.03 % has a discontinuation rate that prevents some patients from receiving the benefits of its IOP-lowering effect.

The proposed new presentation is aimed at improving the ocular surface tolerability, mainly conjunctival hyperaemia, by reducing to one third the content of bimatoprost (i.e. from 0.03% to 0.01%). This leads to an increase in 4-fold of the preservative BAK in order to achieve a greater absorption of the active substance.

5.2 Benefits

Three studies had originally been submitted to justify the efficacy of the new strength for Lumigan (i.e. Bimatoprost 0.01%). Study 020 was not intended to be part of this application and was presented as it was used to obtain information for the dose-finding study.

Study 030 was a supportive trial in which 5 different formulations were compared with Lumigan for 5 days to get some efficacy and safety data and decide the strengths to be used in the Phase 3 pivotal trial (Study 031). This study showed some differences in acute tolerance between doses favouring the lowest ones.

Study 035, which was submitted in response to the CHMP D120 LoQ, compared safety and efficacy of bimatoprost 0.01 % eye drops once daily with vehicle administered once daily for one month in glaucoma or ocular hypertension patients whose IOP was controlled with latanoprost 0.005 % eye drops. An increase in the macroscopic hyperaemia from baseline, i.e. on latanoprost therapy, was observed with bimatoprost (0,18; $p<0.001$), as well as with vehicle (0.02; $p<0.581$). The difference between bimatoprost and vehicle was statistically significant with 0.15 grade ($p<0.009$; 95 % CI 0.04, 0.26). The difference was within the non-inferiority margin of 0.5 grades. Consequently, the non-inferiority criterion was met.

The benefit of the new formulation mainly relies on the results of one pivotal trial (Study 031) in which the non-inferiority of Bimatoprost 0.01% BAK 200 ppm vs. Lumigan 0.03% could be concluded at the pre-specified delta.

5.3Risks

The main rationale for developing the new formulation was to improve the ocular tolerability of bimatoprost by reducing the concentration of the active ingredient, as patients discontinue their treatment with Lumigan mainly due to conjunctival hyperaemia.

Although the adverse effects of glaucoma medications on the ocular surface are likely to be multi-factorial, it is generally accepted that treatment with glaucoma medications containing higher levels of benzalkonium chloride (BAK) resulted in greater corneal damage and conjunctival cell infiltration than medications containing alternative preservatives or with lower levels of BAK.

Bearing in mind that anti-glaucoma medications are life-long therapies, and that often more than one topical therapy is necessary (thus increasing the total daily exposure to BAK), this formulation may improve tolerability, but potentially increase toxicity in the long-term due to the increase in BAK concentration.

In the light of the above, prior to the October 2009 Oral Explanation, the main concerns of the CHMP on the overall Benefit/Risk of Lumigan 0.1 mg/ml can be summarised with the following Major Objections:

1 *Overall, a justification for the Bimatoprost 0.01 % eye drops with the increased concentration of the cornea-toxic agent BAK and with an efficacy, which is not non-inferior to Lumigan was still needed.*

2 *The claimed advantages in terms of tolerability do not overturn the potential disadvantages in terms of ocular surface toxicity and its long-term consequences. Moreover, the concept of the development of Bimatoprost 0.01 % eye drops increasing a toxic ingredient is not appropriate in the context of innovative drug progress. It was claimed by the MAH that such an increment in BAK concentration is needed to reach a similar IOP efficacy. However, the CHMP considered that this has not been demonstrated as lower concentrations have not been tested and the available evidence does not support this theory.*

Allergan responded that they recognised that 200 ppm benzalkonium chloride even in a once day formulation may not be suitable for all patients, specifically patients with evidence of corneal surface damage or where multiple BAK-containing medications are employed. Choice between two

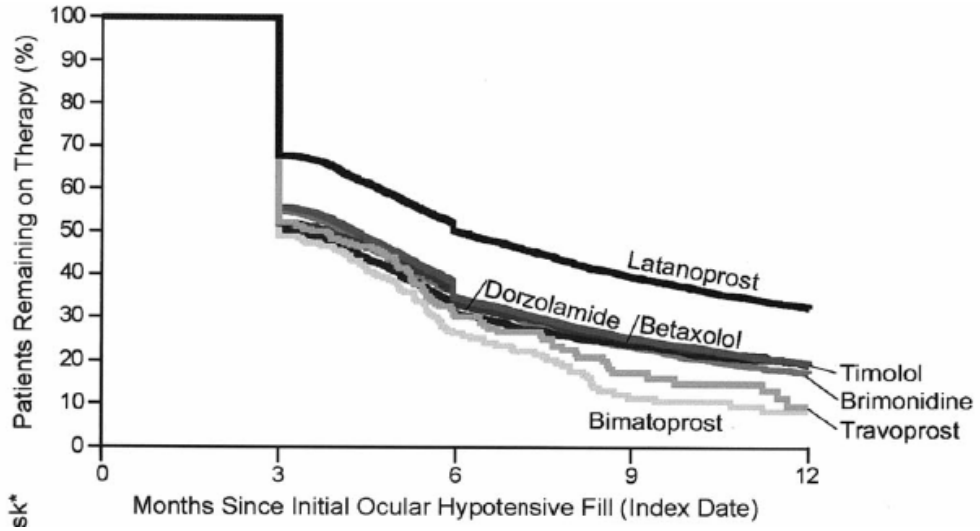
formulations will depend on the patient's ocular status and ability to tolerate the product. Therefore, in the view of the MAH, the therapeutic advantage for this new product was justified.

To specifically address the two major objections outlined above, the MAH pointed out what follows:

Medical treatment has been shown to slow the progression to blindness in patients with glaucoma or ocular hypertension and results from the EMGT have shown that there is a 10% reduction in the risk of visual field progression that for each mm Hg reduction in IOP. Clinical studies have demonstrated that Lumigan 0.03% is a powerful IOP-lowering agent. However, it causes significant conjunctival hyperaemia in up to 44% of patients, causing them to switch or discontinue taking their medication and preventing them from gaining the full benefit of its IOP-lowering effect.

Studies in the clinical practice setting have found an alarming rate of discontinuations with prostaglandin analogues of up to 90% at one year with hyperaemia being among the key reasons for discontinuations. Among the prostaglandin analogues, the rate of hyperaemia and discontinuation appears highest with Lumigan (Figure 1).

Figure 1: Kaplan-Meier plot for time to discontinuation of ocular hypotensive therapies



Source: Reardon et al, 2004

While there are alternative IOP-lowering agents available in the marketplace, the current trade-off for those who cannot tolerate Lumigan is to accept replacing Lumigan 0.03% with another prostaglandin analogue or add an additional glaucoma medication to another prostaglandin analogue to achieve the same efficacy as Lumigan 0.03%.

Therefore, it is Allergan's belief that there is an unmet medical need to provide Lumigan in a different formulation for those patients are willing to take Lumigan consistently. Thus, improving the ocular tolerability of Lumigan 0.03% while maintaining its IOP-lowering efficacy was the primary goal for the development of Lumigan 0.01%.

Allergan spent several years trying to develop a new formulation to achieve our goal, and evaluated a variety of formulations and delivery approaches. Based on dose-ranging studies conducted in the development of Lumigan 0.03%, Allergan ultimately concluded that reducing the concentration of bimatoprost to no more than 0.01% was essential in reducing the ocular surface adverse events. However, these same dose-ranging studies demonstrated that a reduced concentration of bimatoprost of 0.01% would reduce the IOP-lowering effects by approximately 2 mm Hg compared with Lumigan 0.03%, and substantially reduce the product's efficacy. Therefore, a formulation would require a 3-fold increase in ocular absorption of bimatoprost in order to achieve similar aqueous humour concentrations and clinical efficacy to that of Lumigan 0.03%.

Leveraging the physio-chemical properties of bimatoprost to increase penetration through the use of penetration enhancers such as BAK was novel and innovative when this development programme was initiated. Using BAK to safely achieve a 3-fold increase in ocular bioavailability of bimatoprost was considered to be innovative

The approach resulted in achieving the goal of an improved ocular safety and tolerability profile with comparable IOP-lowering efficacy to Lumigan 0.03% in a formulation that contained 67% less of the active drug substance.

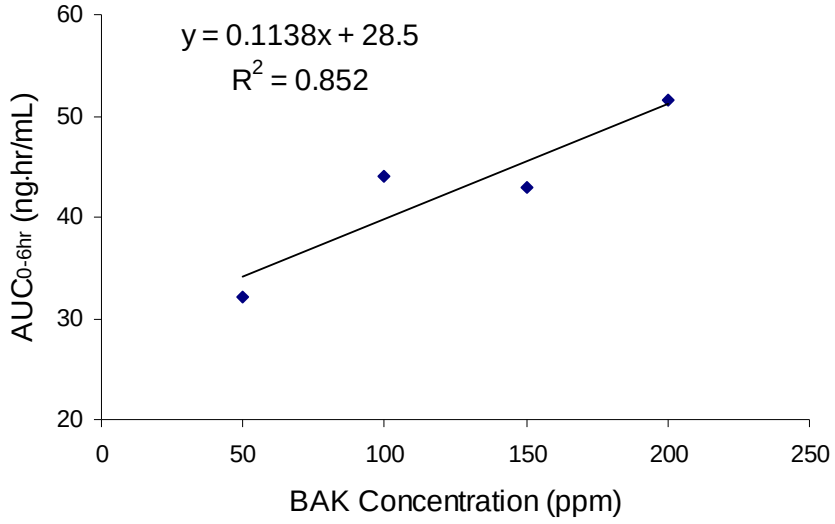
This strategy is also consistent with the EGS guidelines, which reads 'The least amount of medication...to achieve the therapeutic response should be a consistent goal'.

Formulation Rationale and Non-clinical Supporting Data

Topical ocular drugs are absorbed across the corneal epithelium through paracellular or transcellular routes. The hydrophilic character of a drug is a key determinant for the predominant absorption route. Hydrophilic drugs are absorbed primarily through the paracellular pathway and less hydrophilic or hydrophobic drugs predominantly by the transcellular route. Bimatoprost relies on the paracellular route of penetration. Because BAK enhances ocular absorption of hydrophilic drugs by transiently relaxing epithelial tight junctions that temporarily opens the paracellular route to drug absorption, it was anticipated that bimatoprost's penetration would benefit significantly from an increase in BAK. This became the formulation strategy for Lumigan 0.01%.

Rabbit PK studies have provided convincing nonclinical confirmation that BAK enhances bioavailability of bimatoprost in a dose-dependent fashion up to 200 ppm and that a formulation with 200 ppm BAK and only 1/3 the active drug substance could perform comparably to Lumigan 0.03% (Figure 2).

Figure 2 BAK Dose Dependent Effect on Ocular Bioavailability of 0.01% Bimatoprost on Median AUC (Study PK-09-063)



Clinical Rationale for the 0.01% Formulation

During the development of LUMIGAN 0.03% several Phase 2 dose-response studies were conducted using a formulation of bimatoprost containing no preservative. Results of Study 192024-002 (Report previously submitted) showed that bimatoprost 0.01%'s IOP-lowering efficacy was approximately 2 mm Hg less than that of bimatoprost 0.03%, a clinically important difference (Table 5).

Table 5: 192024-002 Overall Difference in Mean Change from Baseline in IOP (mm Hg) at Day 21

Bimatoprost 0.01%/ 0 ppm BAK	Bimatoprost 0.03%/ 0 ppm BAK	DIFF
-4.1	-6.0	-1.9

Report 192024-002, Table 9a. The results presented are an average of the 5 time points measured (hr 0, 4, 8, 12, and 14).

It was also observed from the dose-ranging studies that we could expect a reduction in the incidence of adverse events (particularly hyperaemia) if we could reduce the active drug concentration from 0.03% to 0.01% (Table 6).

Table 6: 192024-001 Adverse Events: Conjunctival Hyperaemia

Bimatoprost 0.01%/ 0 ppm BAK	Bimatoprost 0.03%/ 0 ppm BAK
8.3%	50.5%

Report 192024-001, Table 20a

Therefore, Allergan's strategy was to reduce the concentration of bimatoprost through the use of BAK, with the expectation that the product would achieve the same IOP-lowering efficacy seen with Lumigan 0.03% with the ocular tolerability and safety profile of the 0.01% concentration.

Confirmation of the Desired Clinical Efficacy of LUMIGAN 0.01%

During the development of LUMIGAN 0.01%, the phase 2 (Report 192024-030, previously submitted) and phase 3 (Report 192024-031, previously submitted) studies used the formulation of bimatoprost containing 200ppm BAK. Results of these studies showed that bimatoprost 0.01%'s IOP-lowering efficacy was approximately 0.5 mm Hg less than that of bimatoprost 0.03%, clearly demonstrating an improvement in the IOP-lowering efficacy of bimatoprost 0.01% when formulated with 200ppm BAK (Table 7).

Table 7: Overall Difference in Mean Change from Baseline in IOP (mm Hg) - (across all visits and timepoints)

Lumigan 0.01%	Lumigan 0.03%	Difference
-6.4	-6.8	0.43

Report 192024-031, Table 14.5-6

These results not only provide clinical confirmation that bimatoprost 0.01% achieved clinically comparable results to bimatoprost 0.03%, but also demonstrate that unlike other PGAs, a preservative-free formulation of Lumigan 0.01% would not provide similar efficacy to a preserved formulation.

In addition, based on the clinical development results and supported by the non-clinical PK results, Allergan concluded that a formulation of Lumigan 0.01% containing less than 200 ppm BAK would not have proven comparable in IOP-lowering efficacy to that of Lumigan 0.03%.

Confirmation of the Improved Safety Profile of Lumigan 0.01%

Based on the safety finding from the dose-ranging studies for bimatoprost, it was considered likely that the 0.01% bimatoprost concentration would have a better ocular safety and tolerability profile compared with 0.03%.

Despite not being powered for safety, there were significant differences in favour of Lumigan 0.01%. Bimatoprost 0.01% had a significantly lower incidence of adverse events (overall and ocular), treatment-related or all causality, and had a significantly lower incidence of adverse events related to the ocular surface, treatment-related or all causality. Furthermore, the results showed a better ocular safety for Bimatoprost 0.01% than for Bimatoprost 0.03% in the high-risk population with dry eyes and also in patients not previously exposed to BAK.

In addition, there was a significantly higher rate of discontinuation of Lumigan 0.03% over time. Importantly, this increased rate of discontinuation for Lumigan 0.03% compared with Lumigan 0.01%, as reflected in the relative risk (RR) for discontinuation (6.4% vs. 2.2%, RR: 2.9) is nearly identical to the relative risk for discontinuation seen in the pivotal trials for Lumigan 0.03% compared with timolol (5.3% s. 1.7%, RR: 3.1) providing greater assurance that the reduced discontinuation rates seen with Lumigan 0.01% are valid and offering a reasonable expectation that this formulation would meet the intended goal of improving compliance and persistency.

In conclusion, the interaction between active drug substance, BAK and the ocular surface is a complex one and yet, with these data, Allergan viewed as biologically plausible that an increase in BAK in the presence of marked reduction in active drug substance does result in an improved ocular surface safety profile as seen with Lumigan 0.01%.

5.4 Benefit/Risk Balance

The MAH confirmed that "*LUMIGAN 0.1 mg/ml eye drops, solution is not considered to be a replacement for LUMIGAN 0.3 mg/ml and both products will be retained in the European market.*"

Following the Oral Explanation, the CHMP considered that the MAH sufficiently demonstrated that the Lumigan 0.01 % formulation has an acceptable safety profile, leading to fewer discontinuations than with Lumigan 0.03% while maintaining comparable IOP reduction over 12 months. In addition, a post-marketing study proposed as part of the risk management plan will help obtaining a better understanding of the long-term safety of the new Lumigan 0.01% formulation. This study would preferably be a Randomised Clinical Trial, sufficiently large to pick up rare AEs. Ideally, this study would also include histological data analysis and analyses of the drop-out rate.

The majority of the CHMP considered that the changes introduced in the Product Information and Allergan's commitment to investigate the potential consequences for the target population in a post-marketing study, sufficiently addressed the safety concerns.

The CHMP considered the benefits of Lumigan 0.01 % formulation outweigh the potential risks.

6. Overall Conclusions

A new formulation with better tolerability and less hyperemia was necessary to improve patient compliance. Lumigan 0.1 mg/ml eye drops was developed as lowering the incidence of conjunctival hyperaemia required a lower concentration of bimatoprost (from 0.03% to 0.01%).

The MAH confirmed that Lumigan 0.1 mg/ml eye drops, solution will not constitute a replacement for Lumigan 0.3 mg/ml and both products will be retained in the European market, thus providing physicians with therapeutic options of two formulations – one with a reduced concentration of bimatoprost or one with a low benzalkonium chloride concentration.

The CHMP considered that both Lumigan 0.1 mg/ml and 0.3 mg/ml have a distinct place among IOP-lowering agents.

Allergan recognised that 200 ppm benzalkonium chloride even in a once day formulation may not be suitable for all patients, specifically, patients with evidence of corneal surface damage or where multiple BAK-containing medications are employed. Choice between two formulations will depend on the patient's ocular status and ability to tolerate the product.

To increase knowledge regarding the long-term effects of the new 0.01 % formulation, a post-marketing study will provide the additional safety data. This clinical study should use appropriate numbers of patients, current methodology standards and appropriate safety monitoring in order to detect potential toxic effects on ocular surface. In addition and in order to address the stability of the tear film, an assessment of the tear break-up time (TBUT) as part of the evaluation of the effect of the increased BAK concentration has been endorsed by the Committee. The CHMP emphasized that a randomized controlled trial would be the most appropriate option to evaluate the comparative safety between the two bimatoprost formulations. This study should be sufficiently large to pick up rare AEs. Ideally, this study would also include histological data analysis and analyses of the drop-out rate.

Finally, in order to manage the potential risks associated with BAK, the Lumigan 0.01% SPC and Package Leaflet include relevant warnings, precautions and contraindications and the risk management plan identifies BAK-related corneal toxicity as an important identified risk.

Appropriate statements have been implemented in the SPC and PL and the RMP.

In the light of the approval and forthcoming launch of the new strength, the CHMP considered that the PSUR submission frequency should be annual until otherwise specified by the CHMP.

The procedure is recommended for a positive opinion adopted with divergent positions.